MATERIA MEDICA: PHARMACOLOGY : THERAPEUTICS PRESCRIPTION WRITING

FOR STUDENTS AND PRACTITIONERS

BY

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DEDICATED TO

Professor Henry Hurd Rusby,

BOTANIST, PHARMACOGNOSIST, AND DEAN OF THE FACULTY OF THE NEW YORK COLLEGE OF PHARMACY (COLUMBIA UNIVERSITY)

Dear Doctor Rusby:

Will you do me the honor to accept this dedication as a token of appreciation of your high ideals and of your indefatigable efforts in the cause of pure drugs, and as an expression of my great personal debt to you, my earliest and latest preceptor in the field of "materia medica"?

Sincerely yours,

WALTER A. BASTEDO

PREFACE

This book is an adaptation, for the most part, of lectures delivered at Columbia University. In its preparation I have kept in mind that the physician's reason for the study of remedies is the "treatment of the sick"; and I have laid most stress upon those things that bear on practice, even to the exclusion of some matters of great interest in pharmacology.

But I have endeavored throughout to emphasize the value of research, both in the laboratory and at the bedside, and to point out any discrepancy between the value of a remedy as established by research and its supposed value in therapeutics. For I recognize that, as the result of research, many of the hitherto highly valued drugs are falling into merited disuse; and that some that were of little value because of a wrong understanding of their action have come to have a definite place in our therapeutic armamentarium. Indeed, I have given place to many remedies which I do not recommend, but mention only to condemn.

I believe that, as the outcome of critical laboratory research and the adoption of laboratory methods in clinical research, we are at the dawn of a new era of simple and practical therapeutics, an era in which knowledge will supplant credulity, on the one hand, and skepticism, on the other, and in which fewer drugs will be used but better treatment given.

Both because of the importance of digitalis as a drug and because of the recent great changes in our knowledge of cardiac physiology and therapeutics, I have discussed digitalis at greater length than other drugs; and have drawn my conception of its action as much from recent clinical studies (my own and those of other investigators) as from those of the pharmacologic laboratory. In the chapter on Prescription-writing I have adopted one method for the students to learn; and to avoid confusion have omitted mention of other methods, without any intention to imply that they are inferior.

Recognizing that in a subject which derives so much from research in all the branches of medicine it would be impossible for one person to be equally familiar with all parts, I have drawn freely on the published researches in chemistry, pharmacy,

medicine. But I have felt
impracticable in a work
have omitted credit unless
wise. I have made no attempt
However, I should like espe-
pharmacology by Cushny, Soll-
Meyer and Gottlieb; those on
and Leonard Hill; the
Mackenzie, Pawlow, Herter,
and others; and the Herter

I owe my deepest thanks
whose care about the de-
recording results I believe

W. A. BASTEDO.

CONTENTS

PART I

PART II

PART III

MATERIA MEDICA, PHARMACOLOGY, THERAPEUTICS, AND PRESCRIPTION-WRITING

PART I

INTRODUCTION

"Medicine sometimes cures, it often relieves, it always consoles."

THE physician's calling has arisen from the needs of the sick, a person who is ill desiring the services of some one who can help him to get well. If the sick man cannot be made *well*, he wants as much improvement in his health as possible, so that he may do things; for example, attend to his business, or at least get about. If his health cannot be improved, he wants his comfort promoted and his life prolonged. Thus the objects of the practice of medicine are: to prolong life, to secure comfort, to improve health, or to promote recovery.

The physician accomplishes these objects by doing something for his patients, *i. e.*, by treating them. Therefore his ability to treat his patients successfully is what constitutes his direct personal value for them, and is the ultimate *raison d'être* of the physician's calling. Hence the importance of a familiarity with the available means of treatment, *i. e.*, with *remedial* or *therapeutic measures*.

Therapeutics is the science of the use of remedial measures. When a physician orders a patient to bed, he employs a therapeutic measure. Also when he orders a cold bath, a cathartic, or the application of a mustard plaster; or when he applies a splint to a broken arm, or removes an inflamed appendix, or sits by the bed and calms a nervous patient.

Preventive medicine goes a step further than remedial medicine, in that it designs to prevent the appearance or spread of disease.

The main therapeutic and preventive measures may be grouped as follows:

1. *Hygienic*—those which have to do with cleanliness, disinfection, the prevention of the spread of contagion, ventilation,

the selection of a patient's bedroom, care of bedding, clothing, etc.

2. *Mechanical*—the use of bandages, splints, ligatures, catheterization to empty the bladder, massage, gymnastics, etc.

3. *Operative*—the performance of surgical and obstetric operations.

4. *Physical*—the use of physical agents: heat, cold, light, electricity, *x*-rays, radium, etc.

5. *Hydrotherapeutic*—the external use of water and its modifications: ice, cold water, hot water, and steam, in the form of baths, packs, douches, etc.

6. *Dietetic*—the modifications of diet for the sick.

7. *Suggestive or psychotherapeutic*—suggestion, hypnotism, mental buoying, etc. The psychic influence of a physician is of great importance, and to reassure a patient when she is fearing the worst, to encourage, to stimulate the energies and the will, are among the functions of the physician and are therapeutic measures.

8. *Pharmaceutic*—the use of pharmaceutic or drug remedies.

Materia Medica.—Drug remedies are known collectively as the "materia medica," or medical materials. The science which deals with the properties of drugs is called materia medica, or, more correctly, pharmacology. It is a term that is employed in a broad sense to include everything relating to drugs.

In connection with drugs, there are several great fields of work, the most important being:

1. *Pharmacognosy*—the study of the physical properties of crude drugs. The *pharmacognosist* studies the methods by which drugs are collected, their appearance on the market, the characters by which they may be identified and their quality estimated, their adulterants in the whole and in the powdered state, etc.

2. *Pharmacy*—the art of preparing drugs for use. Manufacturing pharmacy is the art of manufacturing drugs into forms suitable for use in medicine. Dispensing pharmacy is the art of making up prescriptions. The *pharmacist* makes his knowledge tell on the manufacture of preparations and their combination into prescriptions. He studies weights and measures, solubilities, incompatibilities, keeping qualities, chemic reactions, the extraction of active principles, and the making of preparations suitable for use in the practice of medicine.

3. *Pharmaceutic chemistry*—the study of the chemistry of drugs and preparations of drugs.

4. *Pharmacodynamics*, or *pharmacology* (in its restricted sense) the study of the action of drugs. The *pharmacologist*

animal tissues, and *pharmaceutically active*, *i. e.*, capable of causing precipitation or otherwise notable chemic changes in a prescription or preparation. Both kinds are found in cinchona bark, which contains not only quinine and other alkaloids upon which its pharmacologic activity depends, but also tannic acid, an astringent drug. In an ordinary dose of cinchona the tannic acid is too little in amount to have any important astringent effect, and is, therefore, not pharmacologically active; yet if the cinchona preparation is mixed with a preparation of iron, the tannic acid becomes pharmaceutically active and changes the iron salt into ink. Again, the pharmacologically active principles of digitalis are not readily soluble in water, so an aqueous preparation, such as the infusion, would not represent the activity of digitalis were it not for the fact that digitalis also contains a body which possesses the peculiar property of rendering the active medicinal principles soluble in water. This body (digitonin) is, therefore, pharmaceutically active, and as such is important.

A constituent is called an *active principle* when to it may be attributed, either wholly or in part, the physiologic action of the drug.

The *active constituents* of organic drugs may be either:

a. Single chemic bodies, or—

b. Mixtures of such a nature that separation into their components is not advantageous.

The classes of active constituents are:

A. *The Single Chemicals.*
   1. Plant acids and their salts.
   2. Alkaloids.
   3. Neutral principles.
   4. Toxalbumins.
   5. Ferments.
   6. Sugars, starches, and gums.
   7. Tannins.

B. *The Mixtures.*
   1. Fixed oils, fats, and waxes.
   2. Volatile oils.
   3. Resins.
   4. Oleoresins.
   5. Gum-resins.
   6. Balsams.

The last three are natural exudations from plants.

1. Plant Acids and Their Salts.—The citric acid of lemons, the tartaric acid of grapes, benzoic, cinnamic, salicylic, tannic acid, and some of their salts are of interest pharmacologically.

is soluble in 450 parts of water, in 1.5 parts of alcohol or chloroform, and in 16.5 parts of ether; while *atropine sulphate*, the salt in common use, is soluble in 0.38 part of water (less than its own weight), in 3.7 parts of alcohol, in 620 parts of chloroform, and in 2140 parts of ether. Commonly in practice we employ the salts only, but when a solution is to be made in oil, or chloroform, or ether, we must use the pure alkaloid.

Incompatibles.—Alkaloids have extensive chemic affinities, and there are many reagents which are used in the laboratory as tests or precipitants for them. As physicians, however, we need know only their common prescription incompatibles, *i. e.*, those substances which form precipitates with alkaloidal salts, and which we would be likely thoughtlessly to add to a prescription containing an alkaloidal salt. Such common prescription incompatibles are:

1. *Alkalies*, which combine with the acid radicle and throw the less soluble pure alkaloid out of solution (some of the alkaloids are destroyed by strong alkalies).
2. *Tannic acid*, which forms the comparatively insoluble tannate.
3. *Iodine*, *iodides*, and *bromides*, which form the comparatively insoluble iodides and bromides, or double salts.
4. *Mercuric chloride*, which forms insoluble double salts.

In these cases it must be borne in mind that the alkaloid is merely rendered less soluble in water, so if a large volume of water or a fair percentage of alcohol is present, the precipitation may not occur.

Physical Character.—Most of the alkaloids are solids, as morphine, quinine, and strychnine. A few of them are volatile liquids, as nicotine, pilocarpine, coniine, and lobeline, but these latter mostly form non-volatile solid salts, which can be readily handled. Some are crystalline, some amorphous. Some are deliquescent and liquefy in moist air, as pilocarpine chloride; others are efflorescent and lose weight in dry air, as the sulphate of strychnine and the sulphate of quinine. Some are decomposed by the heat of boiling water; others can stand much higher temperatures. Cocaine is decomposed at about 98° C. (just below the boiling-point of water), and its solutions cannot, therefore, safely be sterilized by boiling. Some which will stand a higher temperature for a short time are: aconitine, atropine, brucine, cevadine, codeine, morphine, narcotine, and strychnine; so that aqueous or alcoholic liquids containing these alkaloids may be brought to the boiling-point without fear of harm.

Taste.—The taste of alkaloids is bitter—that of strychnine

on a commercial scale. *Suprarenine*, a synthetic with the actions of adrenaline, is also marketed. In addition, the Pharmacopœia recognizes three bodies which are manufactured from plant alkaloids, viz., *apomorphine*, prepared from morphine by dehydration; *homatropine*, which results from the action of mandelic acid upon tropine, the mother-substance of atropine; and *hydrastinine*, obtained by the oxidation of hydrastine. Two other artificial substances of the Pharmacopœia, *hexamethylenamine*, or urotropine, and *antipyrine*, have close chemic affiliations with the alkaloid group.

That there may be differences in the physiologic actions of the different salts of an alkaloid is suggested by the experiments of O. H. Brown, 1907, on paramœcium. For example, in $\frac{n}{200}$ solutions of quinine salts the paramœcia lived in the sulphate thirty seconds, in the chloride, thirty seconds, in the hypophosphite, fifteen seconds, in the bisulphate, three hundred and thirty seconds. In $\frac{n}{500}$ solution of strychnine salts they lived in the acetate five seconds, in the nitrate, forty-five seconds, in the sulphate, seventy seconds, in the hypophosphite, seven hundred and twenty seconds. They were less readily poisoned by $\frac{n}{100}$ solutions of morphine salts, so the percentage of paramœcia dead at the end of a given time was taken. At the end of two hours, of those in the acetate none were dead, while of those in the valerianate 5 per cent., of those in the sulphate 60 per cent., and of those in the meconate, 90 per cent., were dead.

3. **Neutral Principles.**—Besides acid and basic substances, plants furnish a large number of proximate principles which are chemically neutral. Their names end in *in* (Latin, *inum*), in accordance with the pharmacopœial rule to distinguish them from alkaloids, as stated above. The most important are the *glucosides* (glycosides).

The *glucosides* are a class of bodies which, under the influence of certain agents, decompose and yield some form of sugar, together with one or more other bodies. These decomposing agents may be heat, dilute acids, strong alkalies, enzymes, bacteria, or fungi. Most of the glucosides yield glucose, whence the name; a few of them yield other sugars. Chemically, they are a loose group, and beyond their readiness of decomposition and their power to yield sugar, have no essential characters in common. They follow no rules as to solubility, or taste, or importance, some of them being bitter, some not; some soluble in water or alcohol, some not; some inert pharmacologically, and others, such as the active principles of digitalis, strophanthus, and cascara, being among our most valued remedies. The

the odor and irritant properties characteristic of mustard. This is because, in the presence of water, the myrosin acts upon the sinigrin and splits it up to yield glucose, potassium bisulphate, and allyl sulphocyanide, the last-named substance being the highly irritating "volatile oil of mustard."

Sinigrin		Glucose		Potassium bisulphate		Allyl sulphocyanide
$C_{10}H_{16}NS_2O_{10}K$	=	$C_6H_{12}O_6$	+	$KHSO_4$	+	C_3H_5CNS

As this enzyme is rendered inert by a temperature above 60° C. (140° F.), very hot water should not be used in preparing a mustard poultice or a mustard foot-bath. It is of interest that this volatile oil of mustard, when shaken with alcohol and ammonia water, deposits more than its own weight of crystals of *thiosinamine*, a drug which has been used by injection for the removal of excessive scar tissue. (See Part II.)

$$C_3H_5CNS + NH_3 = C_3H_5CSN_2H_3.$$

White mustard seed also contains myrosin, but instead of sinigrin, it contains another glucoside, *sinalbin*. Under the influence of myrosin in the presence of water sinalbin splits up into entirely different products, viz., glucose, sinapine sulphate (an alkaloidal salt), and acrinyl sulphocyanide (an irritant but non volatile oil).

Phlorhizin (*phloridzin* or *phlorizin*) is a glucoside obtained from the bark of apple, pear, cherry, and plum trees, especially the bark of the root. It is nearly insoluble in cold water, but readily soluble in alcohol and alkaline liquids. Its administration is followed by glycosuria without hyperglycemia, the glycosuria resulting from changes in the kidneys by which they are made unable to keep back the normal sugar in the blood; in fact there is a hypoglycemia. In other words, the "secretion threshold" of the kidneys for sugar (Magnus) is lowered. It is diuretic, this action, according to Loewi (1903), being due to the prevention of kidney reabsorption by the sugar of the urine. It has been used as a test of the functional power of the kidneys.

Besides the glucosides, there are other neutral principles of importance in medicine, such as santonin, aloin, elaterin, chrysarobin, etc. Some of those whose chief characteristic is bitterness, as quassin of quassia, and chamomillin of chamomile, are often spoken of as *bitter principles* or *amaroids*.

Toxalbumins or Toxins.—An extensive class of poisonous protein compounds, of which some occur in plants, some constitute the poisonous products of bacteria, and some are the poisonous agents in the venom of snakes, scorpions, the tarantula, the Gila monster, and other poisonous animals.

Saccharum or *common sugar* (Latin, *saccharum*), $C_{12}H_{22}O_{11}$, is employed to make the various syrups and as a sweetening agent. It is found in abundance in the sap of the sugar maple, in sugar-cane, in sorghum, and in the root of the sugar-beet. It dissolves in half its weight of water and is insoluble in alcohol. It ferments with yeast, but does not reduce Fehling's solution. Solutions administered by hypodermoclysis are rapidly absorbed and are nutritive (Magnus).

Sugar of milk (Latin, *saccharum lactis*), $C_{12}H_{22}O_{11}$, is obtained from milk, and requires for solution five times its weight of water. It reduces Fehling's solution, but does not ferment with yeast. It is not very sweet, and is chiefly used as a nutritive in infant-feeding and typhoid fever. In pharmacy it is employed as a diluent. Cheap brands of sugar-of-milk may contain lactic acid and traces of milk proteins, which form a nidus for bacterial growth, or they may be adulterated with cane-sugar or glucose.

Manna, derived from a tree of the ash family (*Fraxinus ornus*), contains the sugar, **mannite**, $C_6H_{14}O_6$, and is laxative.

Glucose (dextrose), $C_6H_{12}O_6$, not official, is a substance commercially and physiologically of great importance, but of little use in therapeutics. For its nutritive properties it may be added to nutritive enemata or to saline fluids intended for injection into the circulation. Lazarus-Barlow recommends a solution of [illegible] per cent. for intravenous use in shock. Its ingestion as food has proved protective against the fatty degenerations that result from ether, chloroform, and alcohol.

Levulose, $C_6H_{12}O_6$, a form of sugar abundant in honey and some fruits, is a carbohydrate which has been found in many instances to be more easily appropriated by diabetics than are cane sugar, glucose, and many starchy foods (von Noorden). It has been used by Strauss as a test of the functional power of the liver, the assertion being made that if the levulose is recoverable from the urine unchanged, the liver is seriously impaired. In Foster's experiments 3 out of 10 normal cases responded with levulosuria, and only 14 out of 20 cases of well-marked cirrhosis. Churchman, Frey, and others obtained similar results. The test cannot, therefore, be depended upon.

Corn starch (amylum), $C_6H_{10}O_5$, is the starch in common use. It is employed as a dusting-powder for the skin, or for pills to prevent their sticking together, or in the form of *starch water* as a soothing injection in irritative conditions of the lower bowel. To make starch water, the starch should first be hydrolyzed by mixing about a teaspoonful with two ounces of water, boiling until it forms a translucent paste, then diluting with water to one pint. It may be made by simply boiling a teaspoonful of

tannins are given the names of the plants which yield them, *e. g.*, that from cinchona is called cinchotannin, or cinchotannic acid, that from kino is kinotannic acid, etc. The official "tannic acid" is quercitannin, and is derived from oak-galls. It is considered in Part II.

8. The Fixed Oils, Fats, and Waxes.—(*a*) The *fixed oils and fats* are mixtures of the three bodies, olein (liquid), palmitin (semi-solid), and stearin (solid), or close relatives of these, and in addition usually small amounts of other bodies. Olein, palmitin, and stearin are compounds of glyceryl, $C_3H_5\equiv$, with radicles of the various fatty acids. With alkalies they form soaps and glycerin. Castile soap, for example, is made by the action of sodium hydroxide on olive oil, which is nearly pure olein:

$$\underset{\text{Olein}}{C_3H_5(C_{18}H_{33}O_2)_3} + \underset{\text{Sodium hydroxide}}{3NaOH} = \underset{\text{Castile soap}}{3NaC_{18}H_{33}O_2} + \underset{\text{Glycerin}}{C_3H_5(OH)_3}$$

The oils differ from the fats only in the relative proportions of these basal ingredients, the oils having more of the olein, which gives them a liquid consistence at ordinary temperatures, and the fats more of the stearin and palmitin, which make them solid or semi-solid.

The fats and fixed oils have a greasy feeling and are non-volatile, so that they leave a permanent grease-spot. They cannot be distilled, for by heat they are decomposed, with the generation of disagreeable acrid vapors (the familiar odor of burning grease). They are insoluble in water and alcohol (except castor oil and croton oil, which dissolve in alcohol), and are readily soluble in ether, chloroform, and benzin. They are almost all bland, non-irritating substances with nutrient and emollient properties; but on exposure to the air they gradually become rancid by the liberation of odorous and irritating fatty acids. Linseed oil (oleum lini), if exposed to the air in thin layers, will dry like varnish, but most of the oils are of the non-drying type. A few of the fats and oils are of animal origin, *e. g.*, butter, lard (adeps), tallow, suet (sevum), and cod-liver oil (oleum morrhuæ); but the majority are of vegetable origin, as almond, cotton-seed, cocoanut, linseed, olive and peanut oils, and cocoa-butter. These are found chiefly in seeds or in fruits, the best qualities being usually obtained with the least compression necessary and in the cold; the poorer qualities by expression between heated plates. They may also be extracted by a suitable solvent, such as benzin, which is afterward removed by distillation.

Cocoa-butter or *cacao-butter* (oleum theobromatis) is obtained from chocolate-seeds by compression between hot or cold plates.

of sodium hydroxide on olive oil. It is used in the manufacture of pills, soap liniment, chloroform liniment, and saponified tooth powders. (For the chemic reaction see above, under "Fixed Oils and Fats.") Some time ago a proprietary house put out a preparation described as acid sodium oleate. It was extensively prescribed by physicians, though it was nothing but Castile soap containing free fatty acid.

Soft soap or *green soap* (sapo mollis) is prepared from potassium hydroxide and linseed oil, and is employed extensively for cleansing the hands and skin preparatory to operative work. A liquefied form of it is the liniment of soft soap (linimentum saponis mollis), commonly called the "tincture of green soap," made by dissolving soft soap in alcohol and adding oil of lavender flowers.

Lipoids or Fat Allies.—Those of interest to us are *lecithin* and *cholesterin*. *Lecithin* is found in certain animal tissues, especially the central nervous system and the yolk of egg. Of the fatty substances of the latter, it constitutes about 70 per cent. It is a compound of glycerin and choline with stearic, palmitic, and phosphoric acids, and is chemically a complex glycerophosphate. It can be saponified by alkalies. (See Phosphorus.)

Cholesterin, a monatomic alcohol, $C_{26}H_{43}OH$, is a crystalline body found in all forms of protoplasm, but especially in brain tissue. It also occurs in abundance in the yolk of egg, in milk, cream, and butter, and in the bile. Gall-stones are frequently the result of its precipitation in the bile-ducts or gall-bladder. It has been suggested in anemia, especially pernicious anemia, in doses of 15 grains (1 gm.) three times a day; but it is best given in the form of milk and eggs.

Lanolin (adeps lanæ hydrosus), the purified fat of the wool of sheep, mixed with 30 per cent. of water, is made up of compounds of various fatty acids with isocholesterin. It is thus not a glyceryl fat, but a cholesterin fat, and is often classed with the waxes. It is yellowish-white, of soft, sticky consistence, and, unlike the glyceryl fats, cannot be saponified by boiling with an aqueous solution of potash. Its greatest interest for us consists in its power to absorb more than its own weight of water, which makes it of use as an ointment-base for substances in aqueous solution. It is a secretion of the sebaceous type, not absorbable by the sheep's skin. As to its absorbability by the human skin there are conflicting reports, but most observers claim ready absorption. Patschkowski applied an ointment of lanolin and potassium iodide and obtained iodine in the urine in half an hour.

The **waxes** are esters of the fatty acids with hydrocarbon radicles higher in the series than glyceryl. They are of firmer

efficient in protecting the skin from erosion; while the salves containing lard or other animal or vegetable fats become saponified by the alkaline secretions and are useless or harmful. Rövsing recommends vaseline as an injection into the joint in dry arthritis; and Wilkie, the liquid vaseline to prevent adhesions in abdominal surgery. Kerosene and liquid petrolatum are frequently taken internally. They are completely unabsorbed, and serve merely to increase the bulk of the intestinal contents and to soften the feces. They retard the emptying of the stomach.

9. The Volatile Oils.—These are the substances to which many plants owe their characteristic or essential odors. On this account they are often spoken of as "essential oils," or as the "essences" of plants.

They differ from the fixed oils in that—

1. They are volatile, therefore can be distilled and do not leave a permanent grease stain.

2. They do not form soaps with alkalies.

3. They are soluble enough in water to impart to it their odor and taste.

4. They do not become rancid, but on exposure to light and air tend to oxidize and resinify.

They mix freely in any proportions with chloroform, ether, and the fixed oils, and are all soluble in absolute alcohol. Some, like oil of turpentine, require several times their own weight of official alcohol for complete solution. They are all mixtures, some of them quite complex.

Occurrence.—Most of them are found in plants, and each in a definite part of the plant from which it is derived, *e. g.*, oil of orange in the rind of the fruit; oil of cinnamon in the bark; oil of rose in the petals. From these parts they are obtained either by distillation or by means of a suitable solvent, such as benzin, which is afterward removed. Some of the delicate essential oils used in perfumery, as violet and heliotrope, are obtained by spreading the petals or flowers between wax plates, and afterward separating the absorbed oil from the wax.

A few of the volatile oils do not exist in the living plant, and are formed either by the action of ferments on glucosides in the presence of water, as the oil of bitter almonds, or by destructive distillation. These latter are known as *empyreumatic* oils.

For convenience, the volatile oils preëxisting in the plant may be grouped according to their nature, and those developed in the plant part by artificial means may be grouped according to their method of production.

and are added to ointments for the treatment of chronic skin diseases. The syrup of tar (syrupus picis liquidæ), in dose of 15 minims (1 c.c.), is also used as an expectorant.

Creosote is a mixture of phenols and phenol derivatives, obtained during the distillation of wood-tar, and has some of the properties of a volatile oil. The beechwood creosote is considered best for medicinal purposes.

The volatile oils have marked pharmacologic actions, but do not belong to a single pharmacologic group. Their action will be considered in Part II.

10. **The resins** are all, or nearly all, mixtures of several different substances. They are an ill-defined group, forming amorphous masses which have a conchoidal shining fracture. They are insoluble in water and soluble in ether, chloroform, and the volatile oils. Many, but not all, of them are soluble in alcohol, and most of them dissolve in alkali with the formation of a non-detergent resin-soap, which is miscible with water. Their composition is still a subject of study. Some of them, and perhaps all of them, are formed by the oxidation of volatile oils, in association with which in the plant they mostly occur. Common rosin, and the resins of guaiac, jalap, podophyllum, and scammony, are official resins.

11. **The oleoresins** are the natural plant exudates which contain both volatile oil and resin. Balsam of copaiba, Canada balsam, and crude turpentine are examples, common rosin and oil of turpentine being the components of crude turpentine. (These natural oleoresins must be distinguished from the pharmaceutic oleoresins, which are artificial ethereal extracts of oily and resinous drugs, *i. e.*, extracts made with ether.)

12. **The gum resins** are generally oleoresins in natural admixture with gum. They are obtained by the evaporation of the milky juices of certain plants. On rubbing a gum resin with water the gum dissolves, and with the oil and resin forms a milky emulsion. Asafetida and gamboge are examples.

13. **The balsams** are resinous or oleoresinous exudates which contain benzoic or cinnamic acid, or both. These latter impart a "balsamic" odor. Benzoin, storax, balsam of Tolu, and balsam of Peru are official examples. Many fragrant substances are incorrectly called "balsams," *e. g.*, balsam of copaiba and Canada balsam, both of which are oleoresins. In some instances the resins, oleoresins, gum resins, and balsams are the only commercial representatives of their respective plants.

SPECIAL ANIMAL DERIVATIVES

Gelatin (gelatinum) is obtained by acting with boiling water upon certain animal tissues, as the skin, ligaments, and bones, and allowing the solution to dry in the air. It may be obtained in thin, transparent sheets which are permanent if dry, but when moist, readily putrefy. It is soluble in boiling water, and in the proportion of 1 part of gelatin to 50 of water forms a jelly on cooling. In cold water it does not dissolve, though it absorbs water and swells. It is precipitated from solution by tannic acid as a tough, leathery, insoluble mass, a matter of importance in the administration of capsules and of gelatin-coated pills. Besides its uses in pharmacy and as a food, a sterilized 1 per cent. solution in amounts up to 100 c.c. per day has been employed by hypodermoclysis and intravenously in hemorrhage and aneurysm to increase the coagulability of the blood. It is a protein food from which indol is not formed, hence may be valuable in intestinal putrefaction. *Glycerinated gelatin*, a compound of equal parts of gelatin and glycerin, is a rubbery mass, used as a basis for vaginal suppositories and urethral bougies. It melts at the temperature of the body.

Keratin is obtained from horn by dissolving out the albuminous matter with artificial digestion, and macerating the residue in ammonia. It is soluble in alkalies and insoluble in acids, and is employed as a coating for pills and capsules which it is desired to have pass through the stomach without action—the so-called "enteric" pills. Theoretically, if the pills are given after meals, the coating should not dissolve in the stomach, and the medicinal agents should be set free only when the pills reach the alkaline intestinal contents. As a matter of fact, however, commercial keratin is not always proof against disintegration in the stomach, and its coating must be considered unreliable.

PHARMACEUTIC PREPARATIONS

The chemicals and the various mineral, plant, or animal crude drugs may be employed in medicine as such without change, *e. g.*, sodium bicarbonate or cod-liver oil, or powdered digitalis leaves; or they may be made into pharmaceutic preparations, as the rhubarb and soda mixture, the emulsion of cod-liver oil, or the tincture of digitalis.

Pharmaceutic preparations are the prepared forms into which drugs are made for convenient employment in medicine. It is not convenient, for instance, to administer cinchona in the form of cinchona bark. It would be a disagreeable task for a patient to chew the bitter bark, and difficult, because of the inert matter

[illegible] the full physiologic activity of the [illegible], a pharmaceutic preparation, [illegible] activity of the drug, because the [illegible] and it is easily administered. [illegible] drugs—(*a*) may remain un- [illegible] cod-liver oil, rhubarb pills, or [illegible] Dover's powder); or (*b*) may be [illegible] Fowler's solution or Basham's [illegible] to yield their active constituents [illegible] preparations made by extraction. [illegible] employed in the manufacture of other [illegible] water in making chalk mixture, and [illegible] making a belladonna plaster.

[illegible] obtaining the active constituents [illegible] by means of a suitable solvent. [illegible] fiber, cellulose, and other matters [illegible] solvent employed are left behind, so [illegible] of the crude drug appear in the [illegible] solvent is known as the **men-** [illegible] with the different drugs or types of [illegible] water, alcohol, alcohol and water, [illegible] wine, acetic acid, ether, chloro- [illegible] made by extraction are:

[illegible] *infusions* and *decoctions*.

[illegible] in most instances)—*extracts, fluid-* [illegible]

[illegible] *vinegars*.

[illegible] extraction represent the activity of the [illegible] to the active principles, always con- [illegible] inert matter which has gone into [illegible] matter is known as the "extractive," [illegible] as fat, wax, oil, tannin, chloro- [illegible] "extractive" is mostly colloidal in nature, [illegible] the absorption and the activity of [illegible]

[illegible] **of Liquids.**—There are two types of [illegible] chemic and the pharmaceutic. The [illegible] only with weight, as chemic reac- [illegible] regardless of volume. To make a [illegible] 20 grams of the substance to be [illegible] 80 grams of solvent; therefore, 100 [illegible] would furnish 20 grams of the [illegible] the *pharmaceutic percentage liquid,*

Pharmaceutic preparations are **simple or compound.** The simple preparations represent the activity of one drug only; the compound preparations, the activity of more than one drug. For example, rhubarb pills have rhubarb as the only constituent, while compound rhubarb pills contain rhubarb, aloes, myrrh, and oil of peppermint.

Nomenclature.—The simple preparations are given simply the name of the drug prefixed by the name of the kind of preparation, as: Syrup of ginger (syrupus zingiberis), infusion of digitalis (infusum digitalis). The compound preparations have two types of nomenclature. If the active drugs are only two in number, or in some cases three, all are mentioned in the name, as: Pills of aloes and iron (pilula aloes et ferri), elixir of the phosphates of iron, quinine, and strychnine (elixir ferri, quininæ et strychninæ phosphatum). If the important drugs are several in number, especially if one overshadows the others in importance, only one drug is named, and the name of the class of preparation is modified by the term *compound.* Examples are: Compound tincture of cinchona (tinctura cinchonæ composita), which is made of cinchona, serpentaria, and bitter-orange peel; compound licorice powder (pulvis glycyrrhizæ compositus), which contains glycyrrhiza, senna, and sulphur; and compound rhubarb pills, mentioned above.

A few compound preparations of this kind do not bear a drug name, but the name which indicates their *use* in medicine, as compound cathartic pills (pilulæ catharticæ compositæ).

DEFINITIONS OF THE KINDS OF PHARMACEUTIC PREPARATIONS IN COMMON USE

Aqueous Liquids.—*1. Water* (Aqua).—A weak aqueous solution of one or more volatile substances (*e. g.*, peppermint or cinnamon water, chlorine water).

2. Solution (Liquor).—An aqueous solution of one or more non-volatile chemic substances (Fowler's solution).

3. Mixture (Mistura).—An aqueous liquid containing insoluble material (rhubarb and soda mixture). It requires the label, "Shake before using."

4. Syrup (Syrupus).—A dense aqueous solution of sugar with or without medicinal or flavoring substances (syrup of ipecac).

5. Mucilage (Mucilago).—An adhesive aqueous liquid or paste made with gum (*liquid*—acacia; *paste*—tragacanth).

6. Infusion (Infusum).—A liquid obtained by steeping a vegetable drug in water and then straining. The water may be cold, warm, or hot, but the drug is not subjected to boiling.

7. Decoction (Decoctum).—A liquid made by boiling a vegetable drug with water, then straining.

with a solvent, and then removing the solvent by evaporation. An extract is of greater strength than the crude drug. Most extracts are from 5 to 10 times as strong as the drug from which they are made (extract of belladonna).

2. *Powder* (Pulvis).—A dry powdery mixture of drugs (powder of ipecac and opium).

3. *Trituration* (Trituratio).—A powdery mixture of a drug with sugar of milk. The only official trituration is *trituratio elaterini*, of 10 per cent. strength.

4. *Mass* (Massa).—A plastic mixture for division into a number of equal objects, such as pills, troches, etc., and usually obtained by incorporating drugs with an adhesive substance.

5. *Pill* (Pilula).—A rounded or oval body of size to be readily swallowed, and made of cohesive drugs or drugs incorporated with an adhesive substance. Pills may be coated with sugar, gelatin, silver, keratin, or salol. The coating may be white, pink, chocolate-colored, etc.

6. *Troche* (Trochiscus).—A flat body, rounded or lozenge-shaped, intended to be dissolved slowly in the mouth. It contains the medicinal substance, and in addition sugar, flavoring and adhesive material (troches of ammonium chloride).

7. *Compressed Tablet.*—A solid body made by the compression of a powdered drug or mixture of drugs in a suitable mold. With insoluble powders the hard compression retards disintegration.

8. *Tablet Triturate.*—A solid body made of drugs triturated with sugar of milk, and molded with the aid of moisture. They disintegrate as the sugar of milk dissolves.

9. *Confection* (Confectio).—A pleasant-tasting preparation made by mixing medicinal powders and aromatics with syrup or honey (confection of senna).

10. *Granular Effervescent Salt* (Sal Granulatus Effervescens). —A preparation made by adding sodium bicarbonate and citric or tartaric acid to the drug, moistening with alcohol, and passing through a coarse sieve to form granules. It is added to water and drunk while effervescing or later (effervescent sodium phosphate).

11. *Paper* (Charta).—A sheet of paper impregnated with a medicinal substance (niter paper), or bearing it in a state of fine subdivision (mustard paper).

12. *Plaster* (Emplastrum).—A solid mixture which becomes plastic and adhesive on warming; it is spread in a thin layer over muslin, moleskin, etc., for application to the skin.

13. *Poultice* (Cataplasma).—A soft, usually hot and moist paste for external application.

14. *Ointment* (Unguentum).—A soft, fatty (unctuous) preparation which on rubbing melts at the temperature of the body.

Noteworthy Terms	*Approximate Equivalent*	
1 pound avoirdupois is	7000.0	grains
1 pound troy is	5760.0	grains

1 minim of water weighs $\frac{455.7}{480}$ grains = 0.95 grain.

15 grains of water = 16 minims; one grain of water measures 1.05 minims.

An imperial pint is 20 ounces; a United States pint is 16 ounces.

EXACT EQUIVALENTS OF METRIC AND APOTHECARIES' WEIGHTS AND MEASURES ACCORDING TO THE U. S. PHARMACOPŒIA

Volume		
1 c.c.	16.23	minims
1 liter (1000 c.c.)	33.8	oz.
1 minim (♏)	0.061	c.c.
1 fluidram (ʒ)	3.696	c.c.
1 fluidounce (℥)	29.57	c.c.
1 pint (O)	473.18	c.c.
Weight		
1 milligram, 0.001 (mg.)	0.0154	grain
1 centigram, 0.01 (cg.)	0.1543	grain
1 decigram, 0.1 (dg.)	1.543	grains
1 gram, 1.0 (gm.)	15.4324	grains
30 grams, 30.0	462.9	grains
31 grams	478.4	grains
1 grain (gr.)	0.065	gm.
10 grains	0.648	gm.
15 grains	0.972	gm.
1 scruple	1.296	gm.
1 dram (ʒ)	3.89	gm.
1 ounce troy (℥)	31.1	gm.
1 ounce avoirdupois	28.35	gm.

ACTIVE PRINCIPLES AND ASSAY PROCESSES

As might be expected from the different conditions under which plants grow, the different methods of collecting, drying, and preserving drugs, the effects of age on the drug, etc., crude drugs vary in strength. On this account the use of active constituents by themselves has much to commend it, *e. g.*, quinine in preference to cinchona, strychnine in preference to nux vomica, resin of podophyllum in preference to podophyllum. These substances tend also to be more readily absorbed when thus separated from the extractive matter of the crude drug. But in many instances it is impossible or too expensive to isolate the active ingredients in pure form, or there is a preference for the combinations or mixtures as they occur in nature, so pharmaceutic preparations, and even the powdered crude drugs, are much prescribed, even though their active principles are available.

This being the case, it is a matter of great importance that some of the more potent of these drugs and preparations are standardized by the Pharmacopœia to contain a definite percentage of the active ingredients. For instance, when assayed by the process

it shall be of 10 per cent. strength, and it must be made with a certain specified menstruum. Therefore, when the tincture of strophanthus is prescribed, since it is an official preparation, the pharmacist is not entitled to dispense a tincture of any other strength or method of manufacture. On the contrary, if a physician prescribes an unofficial preparation, the pharmacist may dispense one of any arbitrary strength and made by any method convenient, and the physician is left in uncertainty about what his patient is getting.

The United States Pharmacopœia gives information, also, about specific gravity, melting-point, solubilities, tests of identity, tests for impurities or adulterants, the average dose, etc. It is, therefore, an official formulary and book of standards, and is a working guide and dictator for the supplier of drugs, the manufacturer of preparations, and the pharmacist. It is not in any sense a book to be memorized by the medical student; but the choice of its preparations in prescribing favors accurate therapeutics.

The Pharmacopœia is controlled and published by the National Convention for Revising the Pharmacopœia, a gathering of delegates from the various medical and pharmaceutic colleges and state and national societies, and from the Army, Navy, and Marine-Hospital Service. This Revision Convention meets every ten years (1890, 1900, 1910, etc.) at Washington, D. C., to determine the principles to govern the next revision. It also appoints a Committee of Revision to carry out the details of the revision, and administrative officers to issue the new edition when it is ready. Three or four years are then spent by the Committee of Revision in research and in the compilation of the revised book, which becomes official on a fixed date after it is issued. It is known as the Pharmacopœia of 1890, or 1900, etc., the year of the Pharmacopœial Convention. The present Pharmacopœia is the Pharmacopœia or revision of 1900; it became official on September 1, 1905. If a physician wishes to prescribe the formula of a previous pharmacopœia, he must specify on his prescription, "U.S.P. 1880," "U.S.P. 1890," etc.

Because it recognizes so many seemingly needless drugs and preparations, the Pharmacopœia has been much criticized. But it is to be borne in mind that the Pharmacopœia does not consider primarily the usefulness of an article, but merely attempts to standardize those drugs and preparations which are in extensive use by physicians in any part of the country. It must also standardize all substances used in making preparations, whether or not of medicinal value.

The **National Formulary** is a book issued by the American

dependent upon the failure of elimination to keep pace with the ingestion of the drug. The most common drugs to give cumulative effects are *digitalis*, *arsenic*, *mercury*, and *lead*. Lead and arsenic, indeed, are so slowly excreted that they may accumulate in the system even when taken only in the minutest quantities at a time, as from drinking-water that has lain in leaden pipes, or breathing the air of a room with an arsenic color in the wall-paper.

The phrase "pushing a drug to its *physiologic limit*" is sometimes employed when a remedy is given in gradually increasing doses until toxic symptoms begin to appear.

FACTORS WHICH MODIFY THE DOSE

It must be apparent that the ordinary average adult dose is not the dose for every one under all circumstances. Some of the factors modifying the dose are:

1. **Body Weight.**—In pharmacologic experimentation it is customary to estimate the dosage in proportion to the weight of the animal. Within certain limits this should be a good method with humans, and it is the basis of Clark's rule, which assumes that the average weight of an adult is 150 pounds. The rule is—Adult dose $\times \frac{\text{weight}}{150}$. But a patient in bed cannot be weighed, and it takes an expert to guess such a one's weight correctly; and a man with dropsy or an adipose patient would have some extraneous weight to be allowed for. So, as a matter of fact, either on account of our highly organized nervous systems or on account of our ways of eating and drinking and working, or for other reasons, the rule of weight does not seem suitable for practical use.

2. **The Age.** It is evident that the dose for an adult is not the same as that for a child. Yet to establish a working rule is not easy, for not only is there no regular increase in a child's weight according to age, but there is also unequal development of the different systems of the body. The weight rule would be the best but for its difficulty of adoption, and to multiply the adult dose by a simple fraction with the child's age as numerator and the supposed earliest adult age as denominator, will not be correct. It will not do, for example, to take an arbitrary age of twenty or twenty-four as the adult age, and take one-twentieth or one twenty fourth for each year of the child's age. The following table of the average weights at the different ages, taken from Howditch's statistics in 8008 children in Boston, and Paster's of 14,744 children in St. Louis, as recorded by Holt, shows how absurd it is to estimate the dose at two years as twice that at one

the prime of life; and especially must skin irritants, irritant cathartics, narcotics, and depressant drugs be used with caution.

3. **Sex.**—Women usually require smaller doses than men, not only because of their average smaller stature and quieter life, but also because of their greater susceptibility to any influences. During menstruation and pregnancy irritant cathartics, and during lactation saline cathartics, are to be avoided or used with caution.

4. **Temperament, Race, Occupation.**—The patient of highly neurotic temperament is more susceptible than the phlegmatic person. Such difference may be racial, the excitable Italian, for example, being more easily affected than the stolid German; or it may have to do with activity and occupation, the athlete or the man who works all day out-of-doors and is inured to hardship being less readily affected than the man of sedentary habits, the merchant, student, or artist.

5. **Previous Habits (Toleration).**—The morphine habitué can take with impunity a dose of morphine large enough to poison one not habituated, and will obtain no effect from the ordinary dose. An old toper with cirrhosis of the liver will fail to get a medicinal effect from the usual dose of a tablespoonful of whisky.

6. **Idiosyncrasy and Susceptibility.**—*Idiosyncrasy* is that condition in which a patient develops special and unusual effects from a remedy or food. Some people develop a rash after eating strawberries, others after eating lobster, fish, or buckwheat. Sometimes all the members of a family show such an idiosyncrasy to some special article of food, and it is manifest in successive generations. The same is true of drugs. A minute amount of cocaine dropped in the eye or applied to the nasal mucous membrane may cause dangerous symptoms in one patient, though cocaine is used in the eyes and noses of thousands of other patients without any untoward symptoms at all; or a dose of antipyrine may be followed by a marked rash, which recurs each time the drug is taken. These are unusual and unexpected effects, and depend not so much on the size of the dose as upon a specific and unusual hypersusceptibility of the patient toward the drug.

An ordinary increase of *susceptibility* means lowered resistance a condition in which the usual or expected effects are produced by less than the usual amounts. For example, two or three grains of quinine sulphate produce in some people the ringing in the ears, deafness, and headache that in most persons do not come from less than 10 or 20 grains. *Diminished susceptibility* means heightened resistance, the patient showing the usual effects, but only after *larger* doses than usual. For example, some persons can take two or three cups of coffee and then sleep

[illegible] and espe[illegible] narcotics, and depr[illegible]

3. **Sex.** Women usually [illegible] because of their av[illegible] because of their [illegible] During menstruati[illegible] during lactation [illegible] with caution.

4. **Temperament, Race, O[illegible]** [illegible] temperament is mo[illegible] Such difference mo[illegible] example, being more easil[illegible] it may have to do with [illegible] the man who works all day [illegible] being less readily affecte[illegible] the merchant, student, or a[illegible]

5. **Previous Habits.** To[illegible] can take with impunity a do[illegible] one not habituated, and wi[illegible] dose. An old toper with [illegible] medicinal effect from the us[illegible]

6. **Idiosyncrasy and Sus[illegible]** [illegible] dition in which a patient [illegible] from a remedy or food. [illegible] strawberries, others after [illegible] Sometimes all the member[illegible] to some special article of [illegible] generations. The same [illegible] [illegible] may cause danger [illegible]

[illegible] than the total [illegible] resorted to for [illegible] the dose is [illegible] administered, and

[illegible] meals the dose is [illegible] mixture with the stom- [illegible] a larger dose must be [illegible] allows immediate [illegible] as commonly observed [illegible] taken before meals.

[illegible]**stration.**– It goes without [illegible] is less if it is administered [illegible] times a day.

[illegible]ATION

[illegible] manner in which the remedy [illegible]stered to obtain either a direct [illegible] remote local action.

[illegible]en at the place at which the [illegible] in nose, throat, stomach, [illegible] local action, ointments, lini- [illegible] Local remedies may or may [illegible] powder applied to a chafed [illegible] or irritated stomach or bowels. [illegible] membrane and is not absorbed; [illegible] anesthetic effect, must be ab- [illegible]ings or nerves beneath the epi-

[illegible]ction of the drug after its absorp- [illegible] of strychnine on the spinal cord. [illegible]ings in the sweat-glands. [illegible] effect of the drug as it is being [illegible] the bowels by mercuric chloride [illegible] glands or the antiseptic action of [illegible] in the urine. To obtain either a [illegible] local action the drug must be ab- [illegible] constituent of the body fluids.

[illegible]UGS MAY BE ADMINISTERED FOR [illegible] REMOTE LOCAL EFFECT

[illegible] way [illegible] swallowed and [illegible] the drug being intro-

[illegible] the strength of the [illegible] is slowly injected, the [illegible] desired, for the [illegible] the puncture is covered [illegible] medication. In [illegible] and the spot is gently [illegible] a special use for the few drugs [illegible] the liquid into the tissues. [illegible] is usually comparatively small. [illegible] caused by first forcing water

11. The Time of Administ[illegible] [illegible] drops of alcohol to descend [illegible] and absorption dela[illegible] drawn through the lumen [illegible] so if a rapid [illegible] of cocaine and similar [illegible] given. On the contrary, [illegible] action only is desired, the [illegible] action and more ready [illegible] epidermis and gives a *superficial* [illegible] the greater activity of [illegible] *intracutaneous injection*. This

12. The Frequency [illegible] systemic effect is desired.

[illegible] saying that the dose of a [illegible] and disadvantages in hypo- [illegible] every hour or two than [illegible]

ADM[illegible] the drugs get into the tissues: [illegible] more definite.

By *administration* [illegible] because the drug in most instances is to be used. Remedi[illegible] circulation by means of the capil- local action, a systemi[illegible]

The *direct local a*[illegible] administration by mouth is not feasible. drug is applied, as [illegible] patient cannot swallow, as in uncon- urethra, etc. To [illegible] will not swallow, as in drunkenness ments, plasters, etc [illegible] when drugs are taken with suicidal not require to be abs[illegible] alimentary tract is in a state of in- skin, or bismuth su[illegible] non-absorption, as in uncontrollable acts by coating the [illegible] diarrhea. while cocaine, to [illegible] are seldom encountered. They are: sorbed to get at [illegible] abscess formation, either a sterile abscess dermis [illegible] drug, or an infective abscess from un- The [illegible] needle, or skin. tion into the [illegible] injecting the drug into a vein. This would or pilocarpine [illegible] whole dose into the circulation at once, per- The [illegible] disastrous results. To avoid this the syringe excreted [illegible] unscrewed from the needle; if blood oozes from as it is [illegible] it is withdrawn and inserted elsewhere. urethra [illegible] of injecting the drug into a nerve, with result- systemic [illegible] pain. sorbed [illegible] medication has a very restricted employment. [illegible] drugs whose dose in solution is of small bulk THE WAYS [illegible] this method of administration.

[illegible] *hypodermoclysis*, in which a large quantity of saline [illegible] 500 c.c.) is injected into the loose tissues about the absorbed [illegible] abdomen, or into the back below the scapula, or into *B. Sa*[illegible] This amount of liquid causes great separation of

the tissues; and if it is not isotonic, or nearly so, with the blood, or if it interferes by pressure with the circulation of the part, it may result in gangrene or abscess. The writer has seen extensive gangrene follow the injection of 200 c.c. of 2 per cent. solution of sodium carbonate in a diabetic.

D. By Rectum.—Drugs may be placed in the rectum by means of an *enema*, *i. e.*, a rectal injection, or in the form of a suppository or ointment. The uncertainty of absorption and the chance that the drug will be expelled limit the usefulness of this channel and largely restrict it to drugs for local effect only. Proctoclysis is a rectal irrigation or injection intended for both local and systemic effect. It is usually made with saline or medicated saline fluids.

E. By the skin, by inunction, in which an oily or fatty preparation is rubbed upon the skin and left to be absorbed. On account of uncertainty of absorption the dose may vary within wide limits. Mercurial ointment is so used in the treatment of syphilis, and cod-liver oil and cocoa-butter in the treatment of malnutrition.

F. By the Veins, Intravenous Medication.—Drugs administered by a vein act with great promptness, the whole dose passing at once into the circulation. Intravenous medication may be by injection or by infusion. In *intravenous injection* the drug, diluted with a small quantity of normal salt solution, is injected from a syringe, the needle being plunged through the wall of the vein in a slanting direction and toward the heart. When the needle is withdrawn, the valve-like opening thus made usually closes of itself, though sometimes there is a moderate extravasation of blood into the tissues. In *intravenous infusion* a large quantity of warm normal saline solution (500 to 1500 c.c.), or some isotonic liquid, with or without the addition of drugs, is slowly passed into the vein through a suitable nozle. This requires tying a vein, so it cannot be repeated more than once or twice, and is employed only in emergencies.

G. Through the lungs by inhalation—of gas for absorption into the system, as in the use of chloroform or ether as a general anesthetic. (Inhalations of medicated vapors are employed also for a local effect on the respiratory organs.)

THE TIME OF ADMINISTRATION

This is of some importance, *e. g.*, the saline *cathartics* act most rapidly after a period of fasting, so are usually administered before breakfast. *Irritant drugs*, as arsenic or iron or digitalis, are best given after meals, when they become well diluted with the stomach-contents, and come very little in contact

i. e., "pointed to" by the symptoms as the means of treatment to be employed. *Contraindication* has the opposite meaning; it is a condition in which the drug should not be employed.

THE PHARMACOLOGIC ACTION

In this extensive field almost any kind of "aide-memoire" will be of value. It will, therefore, be our general plan to take up in natural succession the actions of each drug as follows: first, its action independently of the body, then its local action, its absorption into the system, its systemic action, its elimination from or disposal by the body, and finally its action (remote local) as it is being excreted. Such a scheme in detail is illustrated in the following chart:

A. *On microörganisms and enzymes*—action away from the body, *e. g.*, antiseptic action.

B. *Local action*—

1. *On skin and adjacent mucous membranes*—nose, throat, eye, vagina, rectum, urethra, bladder.

Eye
- external—conjunctiva and cornea.
- internal
  - pupil.
  - accommodation.
  - eyeball tension.

2. *On alimentary tract:*

Mouth—taste, appetite, saliva, astringency.

Stomach
- on contents—acids, enzymes, food substances.
- on wall—secretion, movements, absorption of food and drugs, pain—emetic, antemetic.

Intestines—on contents, secretion, movements, pain, character of stools.

Liver, pancreas—flow of bile, pancreatic juice, etc.

C. *Absorption of drug*
- at what points or not at all.
- how rapidly.

D. *Systemic action:*

1. *On the circulatory organs:*

Blood—corpuscles, alkalinity, coagulability.

Heart—auricles and ventricles
- rate—slower, faster.
- force—weaker, stronger.
- rhythm—regular or irregular.

Arteries—contracted or dilated.

Arterial pressure—higher or lower.

Always learn through what mechanisms, and how, an effect is brought about. It is not enough to know simply that the heart is faster or slower, or weaker or stronger.

2. *On the respiratory organs:*
   - *Movements* { depth. / rate.
   - *Bronchi*—secretions, muscle.
   - *Cough*—effect of drug depends on whether cough is due to excessive secretion, or lack of secretion, or sensitiveness of throat.
3. *On the nervous system and sense organs:*
   - *Cerebrum*—intellect, emotions, sleep, pain, motor area (motion, convulsions, paralysis).
   - *Cerebellum*—equilibrium.
   - *Medullary and basal centers*—vagus, vasoconstrictor, respiratory, heat-regulating, pupil-dilating, secretory, vomiting.
   - *Spinal cord*—reflexes { muscle tone. / convulsions, paralysis.
   - *Peripheral*—sensory, motor, secretory.
   - *Senses*—sight, hearing, smell, taste, touch.
     - Eye { external / internal } (See Local Action.)
4. *On muscle and bone.*
5. *On metabolism and temperature.*
6. *On secreting glands.*
7. *On genital organs* { male. / female — menstruation, pregnancy, labor, etc.

E. *Elimination or disposal of drug* { how changed in body. / elimination by what route and in what form. / rapidly or slowly—cumulative.

F. *Remote local action*—on excretory organs during elimination—by kidneys, bladder, urethra, skin, bowels, lungs, mammary glands; or in urine, milk, sweat, breath, etc.

G. *After-effects.*

H. *Untoward effects*—unexpected or unusual.

I. *Tolerance*—habit formation.

Such a scheme as the above leads to completeness in the consideration of a drug's action.

B. MECHANICAL APPLICATIONS

These are for local application, and act as protectives in a purely mechanical way. Such are: collodion, adhesive plaster, liquid glass (solution of sodium silicate), plaster-of-Paris (dried calcium sulphate), and the various dusting-powders, such as starch, lycopodium, and talcum, the last being a silicate of magnesium.

SWEETENING AGENTS

These are glycerin, cane-sugar, syrup (see Part I), saccharin, and extract of malt.

Saccharin (benzosulphinid) is an acid anhydride with the formula, $C_6H_4\begin{matrix}SO_2\\CO\end{matrix}\!\!>\!NH$. With sodium bicarbonate it dissolves in water, imparting to the liquid a peculiar sweetness said to be several hundred times as great as that of cane-sugar, though its flavor is not so pleasing as that of sugar. It has been much employed in canning foods, as it is slightly antiseptic and as it obviates the necessity of using the highly fermentable sugar. It is not a food, and lacks the caloric value of sugar. Mathews and McGuigan (1905) showed it to be deleterious in digestion by ptyalin, pepsin, and trypsin. In amounts of over 0.3 gm. per day it has been pronounced harmful by the government Referee Board of Chemists. It is quickly eliminated in the urine in unchanged form, and the lethal dose for a rabbit is in excess of 2½ drams (10 gm.). Its only use in medicine is as a sweetening agent for the use of diabetics, 1 grain (0.06 gm.) with sodium bicarbonate being employed instead of a tablespoonful of sugar.

NUTRIENTS

From a pharmacologic point of view, the only substances coming under this head are gelatin, sugar (see Part I), cod-liver oil, and extract of malt.

COD-LIVER OIL (OLEUM MORRHUÆ)

This is a fixed oil, obtained from the fresh livers of *Gadus morrhua*, and of other species of *Gadus*. It contains faint traces of iodine and bromine and sometimes of phosphorus, but its value in sickness seems to be entirely dependent upon its digestibility as a fat. In other words, it is nothing but a readily digestible fat food, and has no special medicinal virtues. The [illegible]:l obtained from putrefactive livers contains various bases,

skin irritation that may be produced, viz., *rubefacient*, or reddening, *vesicant*, or vesicle-producing, and *epispastic*, or blistering. Beyond this an irritant may produce death of tissue. There are a few drugs, such as mercuric chloride and croton oil, which attack the gland-mouths and produce pustules (pustulant effect), but these are not now employed as counterirritants. In therapeutics, in almost all cases, it is desirable to confine the irritation to the rubefacient degree. In this the superficial vessels dilate, the skin becomes red and warm, and there may be smarting. If the application is too strong or is allowed to remain too long, little vesicles appear, and presently, coalescing, form blisters.

Blistering is very rarely employed as a remedial measure. Until recently blistering of the gums by ammonia was a common practice of dentists; and today a fly-blister over the knee-joint in cases of large inflammatory effusions is more or less employed. However, in almost all cases not only is blistering not desirable, but it is distinctly harmful. For not only is the blister a painful lesion, requiring treatment of itself, but it effectually prevents further applications to the skin at that spot. Hence the more active agents, like mustard and heat, must be carefully watched, especially when the patient is suffering from severe pain or is somnolent or comatose. Unintentional blistering frequently results because of neglect to remove a mustard poultice before going to sleep. In brunets an area of blistering or even vesication may be followed by permanent pigmentation.

The mode of action of counterirritants has been the subject of much speculation, but the recognition in recent years of a relationship between the viscera and certain areas of the skin and body-wall through the nervous system has thrown much light upon the matter. Dana (1887), called attention to "referred pains" as being due to the distribution of the nerves, and Head (1893) and Mackenzie (1902) determined that tenderness of the superficial tissues might be a manifestation of inflammation or injury of one of the internal organs. Recent physiologic studies have shown that pain is elicited only in structures supplied by the cerebrospinal nervous system, and that viscera supplied by sympathetic nerves have no proper pain sense. The apparent pain in inflamed viscera is thus due to a reflex effect through the cerebrospinal nerves. Hence the tenderness of appendicitis is mostly localized at one point, though the actual situation of the appendix is very variable; the tenderness of cholelithasis is spread over an area much greater than that of the gall-bladder; and in pulmonary tuberculosis the superficial tissues are sometimes so tender as almost to preclude examination by percussion. Hertz (1911) concluded that pain in disease of the alimentary

tract may be situated in the skin, muscles, and connective tissues. Sherrington (1909) demonstrated that on cutting certain nerves passing to the intestines and stimulating the central cut ends, the abdominal muscles contract in a definite manner. Also, it is a well-known physiologic fact that pain tends to cause contraction of the splanchnic arteries.

These findings all go to show a very close relation, through the nervous system, between the tissues of the body-wall and the contained viscera, and tend to explain how irritation of a superficial area may have a decided effect upon a deep-lying or even remote viscus which is in no way in direct connection or contact with the irritated area. In this way may be understood the expulsion of flatus by the intestines as the result of a turpentine stupe applied to the abdomen, though the intestines have no direct anatomic connection with the anterior abdominal wall; or the effect of a mustard foot-bath in pelvic congestion; or of a mustard paste on the chest in pleurisy or pneumonia. It has been demonstrated also that cold and heat act reflexly and not directly, for the superficial application of an ice-bag or a hot-water bag has little if any effect upon the temperature of a deep-lying viscus.

Fig 1.—Areas in which pain is sometimes felt: (*A*) In cardiac affections, (*B*) in affections of the stomach; (*C*) in affections of the liver, stomach, or duodenum; (*D*) in affections of rectum or uterus (after James Mackenzie, in "Symptoms and Their Interpretation").

As working theories, Head and Hertz adopt the segmental relation, *i. e.*, that the spinal cord and brain are in regular segments, and that a lesion affecting a nerve from a given segment affects all the nerves whose centers are in that same segment. "Head's areas," mapped out on the skin by Head as being the areas of tenderness in the various visceral affections, have not, however, been at all constant, and Mackenzie has pointed out that in visceral lesions pain and tenderness do not appear in the

whole distribution of any one segment, but in limited areas in the distribution of two or several segments. Therefore, Mackenzie suggests a *regional* relation rather than a segmental one. The good action of these reflexes may be the result of a conferred hypersensitiveness to stimuli, to reflex changes in the circulation, or to other so far unknown effects.

Rubbing the back will sometimes distinctly affect the viscera, and Mackenzie's picture herewith suggests a reason for the success, in some instances, of the osteopathic plan of manipulating the spine and its neighborhood.

That counterirritation may act in other ways is also possible, for it is well known to every one that pain in a sensitive place results in a diminished sense of pain in a less sensitive region. It is probable, also, that the psychic suggestive effect, as of a thermocautery, may at times be important, and that in the treatment of muscular or other tissues in direct contact with the skin changes in the local blood-supply may account for the remedial effect. In this connection it is of interest that Lazarus-Barlow has shown that a muscle on the same side as a blister has a higher specific gravity than the corresponding muscle on the unblistered side. And Wechsberg has demonstrated that when abscesses were experimentally produced in rabbits' legs, they were less extensive and healed more rapidly on the side to which counterirritants were applied. Oliver found that a mustard paste over the liver sent the blood-pressure from 105 to 135, and Roth, that a large hot application to chest and abdomen sent up the pressure about 8 mm. in each of two cases. But Wood and Weisman (1912) find that irritation of the skin of the hand by a mustard-bath just short of producing dermatitis does not materially increase the rate of blood-flow in the hand, the skin redness being presumably not accompanied by a change in the caliber of the deep-lying arterioles.

We may sum up, then, by repeating that the good effects of counterirritation may be due to: (1) A segmental or regional nervous relation between superficial tissues and the viscera. (2) The countering effect of a superficial pain over a deep-seated one. (3) A direct circulatory effect. (4) A psychic effect.

Preparations.—The more commonly employed counterirritant measures are: heat, cold, dry-cupping, and drugs.

Heat is applied as an electric pad, a hot-water bottle, a hot stone or flat-iron wrapped in cloth, or a poultice, when the desire is to apply something that will keep hot a long time. For a sudden application of extreme heat the thermocautery or the stupe may be employed. A *stupe* is a towel wrung out of very hot water; a turpentine stupe is made by sprinkling 15 or 20

pentine, *tincture of iodine*, *ammonia*, *capsicum*, and *mustard*. The epispastics are: *ammonia water* (used by dentists for blistering the gums) and *cantharides cerate*.

Mustard (sinapis) is the ground seed of black mustard (*sinapis nigra*). Its use depends upon the development of an irritant volatile oil when the mustard flour is mixed with water. (See Glucosides, Part I.) It may be employed in the form of a mustard-leaf (charta sinapis) dipped in tepid water, or as a thin mustard paste made by wetting a mixture of mustard and flour with tepid water and wrapping in cheese-cloth. For an adult the paste may be made of one part of mustard to two or three of flour, according to the sensitiveness of the skin; for a child, one part to four or five of flour. A mustard paste usually reddens sufficiently in ten to thirty minutes, and its effect must be watched to prevent blistering. As soon as the skin is thoroughly reddened the mustard should be removed. Sometimes, with the idea of preventing blistering, white of egg is mixed with the paste, or vaseline is smeared over the skin at the site of application. Whether such measures are efficacious or not we are unable to say. In pelvic congestion with suppressed menstruation a mustard foot-bath is sometimes employed. It is made by adding a tablespoonful of mustard to four quarts of *warm* water. A mustard-bath for infants is prepared of half this strength. In all mustard preparations very hot water should not be used, as this destroys or retards the activity of the enzyme which forms the irritant volatile oil. The enzyme is destroyed at 60° C. (140° F.). It is to be borne in mind that the "hotness" of a mustard-bath should be entirely due to the mustard oil developed, and not to its temperature as recorded by the thermometer. Cases of poisoning by mustard give the symptoms of volatile oil poisoning. (See Carminatives.)

Cantharides (cantharis) is the dried and powdered brilliant green beetle, *Cantharis vesicatoria*, or Spanish fly. Its active constituent is cantharidin, an acid anhydride which forms soluble salts with alkalies. The "fly-blister" is a piece of adhesive plaster spread with cantharides cerate. About its only employment is in large inflammatory collections of fluid in the knee-joint, as in acute rheumatism. A fly-blister about two inches in diameter is applied to the skin for twenty minutes, then removed, and replaced by a flaxseed poultice. A large amount of serum collects beneath the skin and is removed by pricking the skin.

Internally, the 10 per cent. tincture has been employed as an emmenagogue in dose of 5 minims (0.3 c.c.). From its use to produce abortion, and its administration with the fancied purpose

less and odorless, but irritating to mucous membranes if continuously applied. Practically its only use at present is in psoriasis, the 5 per cent. ointment being employed. This is not used about the face, as it may cause irritation of eyes, nose, and mouth.

THE DIGESTIVE FERMENTS

PEPSIN

Pepsin (pepsinum) is an enzyme usually obtained from the fresh mucous membrane of the hog's stomach. It is almost entirely soluble in 50 parts of water, and more so in water acidulated with hydrochloric acid. It acts in a weakly acid medium to change the insoluble proteins of the food into soluble protein. It is destroyed by 0.01 per cent. sodium hydroxide (Sollmann), and it is inhibited by strong acid, human pepsin, for example, ceasing to act when the hydrochloric acid reaches 0.3 per cent. By the U.S.P. test it must be able to change 3000 times its weight of coagulated egg-albumin into soluble protein. In other words, one grain of pepsin can digest at least 6¼ ounces of coagulated egg-albumin. Dr. Gies has told me of a specimen in existence 200 times as powerful as this. The U. S. P. test calls for digestion at 125.6° F. (52° C.) for two and one-half hours in water containing one part of absolute hydrochloric acid in 3000.

Pepsin is, therefore, a highly powerful substance; and it would be a very important therapeutic agent were it not for the fact that in almost all classes of digestive disturbances it is a superfluous remedy. For by extensive tests with human gastric contents it has been found that, except in the not very numerous cases of achylia gastrica with atrophy of the gastric mucous membrane, the stomach rarely fails to secrete its specific ferments. Hence its only use as a digestive agent is in atrophic cases, and in these it is not always efficient. (See Pancreatin.) It may be given in capsules, 5 grains (0.3 gm.) at the beginning of a meal and 5 grains at the end, with hydrochloric acid in proper dilution.

Pepsin regularly contains some rennin; its solutions, therefore, will coagulate milk.

PANCREATIN

Pancreatin (pancreatinum) is usually obtained from the fresh pancreas of the hog or ox. It contains the specific ferments of the pancreas, and represents its external secretion. There is no evidence that it also represents the internal secretion, and it has no power to check pancreatic diabetes. Its notable actions are those of the enzymes, trypsin, amylopsin, and steapsin. It acts best in an alkaline medium.

ness and thick consistence it is a good vehicle for cod-liver oil, cascara, and other strong-tasting drugs.

There are also marketed some "*extract of malt*" preparations which are really malt liquors of the nature of beer. They contain about 2 per cent. of alcohol, by volume, and much nutritive extractive. In some cases they are made bitter with hops. They have very feeble digestant power for starch.

Taka-diastase, a ferment with diastatic properties, is obtained from a mold, *Aspergillus oryzæ*, which grows in Japan upon the rice plant.

Papain is an enzyme obtained from the juice of the unripe fruit of *Carica papaya*, a South American papaw plant. It can digest albumin in a medium that is alkaline, neutral, or acid, but acts best in one that is slightly acid. It has no special indications.

Ingluvin is the dried lining membrane of the chicken's crop. Its digestive power is not very great. It has been given in doses of 5 grains (0.3 gm.) after each meal in the nausea and vomiting of pregnancy, but its use is purely empiric.

Secretin, owing to its unstable nature, has not as yet come into general therapeutic use.

Hormonal is a preparation from the spleen of the rabbit. It is said to contain the same peristaltic hormone as the gastric mucous membrane. Reports as to its value differ widely, but a number of authorities have obtained good and continued action of the bowels in post-operative tympanites and obstinate chronic constipation. It tends to cause headache and a marked fall in blood-pressure, and anaphylaxis has occurred. Rosenkranz reported collapse from 10 c.c. intravenously; Frischberg reports collapse from 20 c.c., with chill and a temperature of 105.8° F. From the intravenous use, Hoxie obtained good results in two out of three patients with chronic constipation, and no effect from the intramuscular injection. Dittler and Mohr attribute the peristalsis to the fall in pressure, and question the presence of a hormone. It is given in dose of 15 to 40 c.c. intravenously or intramuscularly, the latter being painful. For intravenous use it is marketed pure, and for intramuscular use, with 0.25 per cent. of beta-eucaine chloride. Zuelzer claims that the collapse was due to albumose, and that at present only albumose-free hormonal is marketed.

As there is a tendency for these ferments to destroy one another, mixtures of digestive ferments, especially those which

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thrombosis. But Rudolf and Cole (1911) have determined that citric acid administered by mouth does not essentially influence the time of coagulation of the blood either in typhoid fever or in other conditions; and Addis (1909) has shown that in the amounts which it is possible to administer therapeutically the drug does not affect coagulability. Weiss says that it requires at least 5 or 6 grams a day to have any effect. Citric acid also, according to Hofmeister, lessens the viscosity of the blood by converting sols into gels.

Formic acid (acidum formicum, HCOOH) has been employed locally and internally in rheumatism. It is present in the secretion of the sting of the bee, and has been employed by allowing bees to sting the involved part.

Acetic acid (acidum aceticum, CH_3COOH) is the essential ingredient of vinegar. The Pharmacopœia recognizes *glacial acetic acid* of 99 per cent. strength, which is used for the removal of warts; *acetic acid*, of 36 per cent. strength; and *diluted acetic acid*, of 6 per cent. strength. The last is of the strength of good vinegar. A 2 per cent. solution is also employed as an intrauterine hemostatic in postpartum hemorrhage. *Trichloracetic acid*, CCl_3COOH, is strongly caustic, and is employed in the removal of warts, small nevi, and hypertrophied tissue, such as occurs in the nose. The **acetates** are freely soluble in water, are readily absorbed, and by changing to carbonate act as agents to alkalinize the blood. They are diuretic, and their intravenous administration is followed by a fall in arterial pressure, and dilatation of the kidney arterioles.

Lactic acid (acidum lacticum, $C_3H_6O_3$), obtained by fermentation from sugar-of-milk, finds its chief use in 10 to 50 per cent. solution in glycerin as an application to tuberculous ulcers of the throat.

Recently, on the theory that putrefactive germs in the intestines are inhibited by lactic-acid germs and their products, the lactic-acid drinks have come into extensive use both by physicians and the laity. Such drinks are: zoolak, fermillac, kumyss, sour milk, buttermilk, etc. Special strains of lactic-acid bacteria are also sold to be used in making sour milk, or to be swallowed in the form of capsules, tablets, or liquids. Whether or not this form of medication has any real value is still a moot question, some more recent researches indicating little if any use for the drinks except for their nutritive constituents. Lactic acid drinks are prone to induce attacks of gastric hyperacidity, and to bring on rheumatic manifestations in those subject to rheumatism. A recent claim that they are of value in diabetes requires extensive clinical testing.

Coagulation of the Blood.—It is an old observation that calcium salts added to the blood outside of the body, or intravenously, increase its coagulability and lessen its coagulation time. But it is still a question whether calcium salts administered by mouth have such an effect. Wright and Paramore (1905) found a distinct difference within an hour or less; but Rudolf and Cole (1911), after a very careful series of studies, have come to the conclusion that "the free exhibition of calcium lactate by mouth has no appreciable effect upon the coagulation of the blood"; and Van Lier (1912), after taking the coagulation time in 40 persons before and after administration of calcium lactate, has arrived at the same conclusion. Addis (1909) found that calcium salts administered by mouth increased the ionizable calcium of the blood, but the increase, even from large doses, was considerably less than that required to alter the coagulability. The use of calcium salts as local hemostatics is a failure.

In the *clotting of milk* by rennet, calcium is a necessity. (See Rennet.) However, if much of an alkaline calcium salt, such as in lime-water, is added to milk, the alkalinity will check the rennet action and the milk will not coagulate. It is probable that, as a rule, any ordinary amount of lime-water is neutralized by the acid of the gastric juice, with the formation of calcium chloride.

Januschke (1910) has shown that pleural effusions may be checked by subcutaneous injection of calcium chloride, and Chiari found that *transudation and edema* were favored by the removal of calcium, which normally serves to check the permeability of the vessels. These experimenters were able to check pleural effusion resulting from diphtheria toxin, and to reduce the conjunctival edema resulting from the application of irritants. Other authors have reported good results from the use of calcium salts in serum-sickness from diphtheria antitoxin, in angioneurotic edema, in chilblains, and in other conditions suggesting abnormal permeability of the vessels.

In the intestines calcium salts have been found to retard or check peristalsis and to prevent the action of some of the cathartics.

Therapeutics.—Precipitated chalk is used largely for cleaning teeth. Prepared chalk is used as an antacid and in diarrheal conditions. Lime-water is used as an addition to milk to render it more palatable and more readily borne by the stomach, and to increase its calcium content for growing children. Lime-water has also been added to skin lotions for eczema and dermatitis.

Calcium chloride and calcium lactate have been employed, with questionable results—(*a*) In hemorrhagic conditions, as

hemophilia, the purpuras, the hemorrhages of typhoid fever and tuberculosis, melæna neonatorum, etc. They are not indicated unless the coagulability of the blood is distinctly reduced. (*b*) In tetany and the nervous manifestations following parathyroidectomy or oxalic acid poisoning. (*c*) In nervous diseases with hyperexcitability, as epilepsy. (*d*) In serum sickness, urticaria, angioneurotic edema, chilblains, pleurisy with effusion, etc. (*e*) In bronchial asthma, to lessen nervous excitability and angioneurotic swelling of the bronchi.

Either the lactate or chloride may be used in dose of 5–10 grains (0.3–0.7 gm.) three times a day. The bitter saline taste of the chloride may be masked by peppermint. Hypodermatically, a 4 per cent. solution may be employed. Intravenously, a 1 per cent. solution of the chloride may be given in amounts of 100 c.c., or a 0.2 per cent. solution of the lactate in normal saline in amounts up to 500 c.c. The chloride must not be confused with the antiseptic, chlorinated lime (chloride of lime).

Calcium Poisoning.—Large doses intravenously at first increase the contractility of the heart, but soon bring about its stoppage, the arteries being contracted and the pupils pin-point. Human cases are not reported.

The Antacids Not of Alkaline Reaction

These do not neutralize acids, so are not locally antacid; but in the blood and tissues they break down into carbonates, and so increase the alkalescence of the blood. They are, therefore, systemic alkalinizers. These compounds are the acetic, citric, and tartaric salts of potassium, sodium, and lithium.

The **potassium and sodium acetates,** $KC_2H_3O_2$, $NaC_2H_3O_2$, and the **potassium, sodium, and lithium citrates,** K_3-,Na_3-,Li_3,-$C_6H_5O_7$, are freely soluble in water. **Potassium bitartrate,** or cream of tartar ($KHC_4H_4O_6$), is of acid reaction, and soluble in 200 parts of water. **Potassium and sodium tartrate,** or Rochelle salts ($KNaC_4H_4O_6$), is very feebly alkaline and is soluble in 1.2 parts of water.

The **acetates** are readily absorbed, and are alkalinizing and diuretic. Dose, 30 grains (2 gm.).

The **citrates** and **tartrates** are absorbed with some difficulty, and, as a consequence, are more or less cathartic. A portion, however, is absorbed, and this acts as an alkalinizer and diuretic. Tartrates have been recovered from the urine, but not citrates.

The **citrates** (see Citric Acid), through their affinity for calcium, will retard or prevent the coagulation of the blood and the rennin clotting of milk. They have been employed without any decided success in the late weeks of typhoid fever to lessen the

tendency to thrombosis. *Lithium citrate*, in the form of effervescing tablets, each containing 5 grains (0.3 gm.), has been much employed to make a palatable effervescing alkalinizing drink. One tablet may be dissolved in a glass of water. *Sodium citrate*, 1 grain (0.06 gm.) to each ounce (30 c.c.) of milk, has been used in infant-feeding to reduce the density of the curd.

Potassium bitartrate (cream of tartar) is not readily soluble in water. It forms Rochelle salts in the duodenum, and is laxative. It is a constituent of Imperial drink. (See Citric Acid.)

The hospital "A. B. C. mixture" is an aqueous solution of which each teaspoonful contains 10 grains (0.7 gm.) each of the acetate, bicarbonate, and citrate of potassium.

CARMINATIVES

A carminative is a remedy which tends to overcome flatulency, that is, distention of the stomach or colon with gas. The aromatics, which depend for their action upon a volatile oil or resinous constituent, form the great bulk of the class; but alcohol, the distilled liquors, chloroform, ether, ammonia, carbonic acid, as in mineral waters and champagne, and many other local irritants have strong carminative properties. We shall take up here the action of the aromatics.

Pharmacologic Action of the Aromatics.—*Microörganisms.*—They are antiseptic, some of them strongly so, as oil of eucalyptus. Their use as antiseptics, however, is very limited, because of their slight solubility in water. In infected tooth-cavities the dentists use oil of cloves, or its stearopten, eugenol, or oil of cinnamon.

Skin and Mucous Membranes.—They are general protoplasmic irritants, so are irritant to both skin and mucous membranes. Applied to the tongue they have a biting effect, and in the eye cause smarting. Rubbed into the skin they are rubefacient, *i. e.*, produce local dilatation of the skin-vessels, with redness and warmth of the part. It is probable that they also stimulate the sensory nerve-endings and later depress them, for there is more or less biting and tingling, followed in a number of instances by partial anesthesia or numbness. Peppermint, and its stearopten menthol, distinctly depress the sensory nerve-endings, but at the same time stimulate the ends of the temperature nerves which appreciate cold (Ioteyko, 1903), hence they give a combined feeling of numbness and coolness.

Alimentary Tract.—Many of them are pleasantly aromatic, and these are used as flavors, especially in the dilute forms of the official waters and spirits. They tend to promote the appetite, but in undiluted form are irritant enough to induce a protective

flow of saliva. In the stomach they are local irritants, and if given in sufficiently concentrated form, dilate the vessels and produce hyperemia, thus giving a feeling of well-being in the stomach region. At the same time they stimulate motor activity and the expulsion of accumulated gases. The stronger they are, the more prompt is their action. It is generally believed that there is some stimulation of secretion, so that they are contraindicated in hyperacidity; but Korczynski (1901) found that from pepper and mustard there was not only no increased acidity or quantity of the gastric juice, but even a diminution. It may be that, like alcohol, they increase the gastric secretion through an action in the mouth. There seems to be some furtherance of absorption by the stomach, presumably owing to the active hyperemia. Thus the functions of motion and absorption are stimulated, but probably not that of secretion unless they promote appetite.

On the intestine there is a reflex effect, and Hertz (1910) has observed by the *x*-rays that very promptly following the administration of a strong carminative by mouth colon peristalsis is set up. This is a reflex action, and it tends to cause the expulsion of accumulations of intestinal gas, and to overcome colic or griping. For this last action these drugs are regularly added to irritant cathartics as "correctives."

Absorption is rapid from stomach and duodenum.

Nervous System.—From the local irritation in the mouth or stomach there is a general reflex stimulation of the vasoconstrictor, the accelerator, and the respiratory centers, so that respiration is deepened and arterial pressure raised, and momentary feelings of faintness are overcome. In this way carminatives act as restoratives. There is also, after absorption, an apparent cerebral stimulation which may be effective in overcoming hysteria and other conditions of nervous instability.

Circulation.—Besides the reflex stimulation, there is flushing of the skin from dilatation of the cutaneous arterioles.

Genital Organs.—In strong doses these oils tend to be emmenagogue and abortifacient, and many of the cases of poisoning by pennyroyal, rue, savine, and tansy have come from attempts to produce miscarriage. Frequently the victim has died in agony without the abortion occurring, or has developed a severe colitis. Whether the influence on the genital organs could be a factor in overcoming hysteria has not been studied.

Elimination.—Part is oxidized in the body, and the remainder is eliminated in the urine and the breath, mostly in more or less changed aromatic forms. For example, the odor of the breath of the whisky-drinker is not that of either alcohol, whisky, or fusel oil, but of a derivative of the fusel oil. The urine from

ing operations. By mouth, oil of turpentine, 10 minims (0.07 c.c.) in capsule, or asafetida, 5 grains (0.03 gm.) in pill or tincture. By rectum, oil of turpentine, ½ ounce (15 c.c.), or tincture of asafetida, 1 dram (4 c.c.), added to a soapsuds enema or to 8 ounces or more of infusion of chamomile (an aromatic bitter).

5. *As anthelmintics*—oil of chenopodium for round worms and oil of thyme or thymol for hookworms.

6. *As stimulants to mucous membranes of nose and throat*—eucalyptol, camphor, and menthol, mixed together and inhaled, or diluted with liquid petrolatum and used as a spray.

7. *As antiseptics and anesthetics*—oil of cloves or oil of cinnamon in decayed tooth, a drop on cotton. Eugenol, the stearopten of oil of cloves, is also used.

8. *As counterirritants*—camphor, capsicum, and menthol, and the oils of mustard, rosemary, and turpentine.

9. *As stimulants in chronic skin diseases*, such as eczema—the oils of cade and tar in the form of ointment.

10. *As stimulants to the growth of hair*—the oil of mace.

11. *As antirheumatics*—methyl salicylate and the oils of birch and wintergreen, externally as a liniment, and internally in 5-minim (0.3 c.c.) capsules.

12. *As antihysterics*—asafetida, camphor, musk, sumbul, and valerian.

13. *As anti-asthmatics*—powdered cubebs smoked in cigaret form.

14. *As bronchial stimulants (and perhaps antiseptics)*—creosote, 5 minims (0.3 c.c.), oil of turpentine, 10 minims (0.7 c.c.), terebene, 10 minims (0.7 c.c.), and syrup of tar, 10 minims (1 c.c.).

15. *As diuretics*—oil and spirit of juniper; the fluidextracts of buchu and uva-ursi, 1 dram (4 c.c.).

16. *As urinary antiseptics*—the oils of copaiba, cubebs, and sandalwood, and balsam of copaiba, 5 minims (0.3 c.c.).

17. *As emmenagogues*—apiol, from oil of parsley, and the oils of pennyroyal, rue, savine, and tansy, 3 minims (0.2 c.c.).

18. *In leprosy*—chaulmoogra oil, 5 minims (0.3 c.c.), two or three times a day.

A number of these will be referred to elsewhere in their respective therapeutic groups.

For simple carminative action the spices are much used, and usually in combinations of several carminatives, as in the compound tinctures, compound spirits, and the aromatic fluidextract. A favorite hospital dose for flatulence is compound spirit of ether, aromatic spirit of ammonia, compound tincture of lavender, and spirit of chloroform, of each, 15 minims (1 c.c.).

cum, cardamom, cinnamon, ginger, lemon-peel (limonis corticis), musk (moschi), valerian, vanilla.

8. *The compound tinctures* are: *Compound tincture of cardamom* (tinctura cardamomi composita), containing cardamom, cinnamon, and caraway.

Compound tincture of lavender (tinctura lavandulæ composita), containing oil of lavender, oil of rosemary, cinnamon, cloves, and nutmeg.

Ammoniated tincture of valerian, a tincture of valerian made with aromatic spirit of ammonia as the menstruum.

9. *The fluidextracts* are: Bitter orange-peel, buchu, calamus, capsicum, cubebs, cypripedium, eucalyptus, ginger (zingiberis), savine, sumbul, uva-ursi, valerian, and the aromatic fluidextract (fluidextractum aromaticum). The last is a fluidextract of aromatic powder (pulvis aromaticus) which contains cinnamon and ginger, each, 35 parts, and cardamom and nutmeg, each, 15 parts.

Doses.—These vary somewhat. Where the drugs have no other marked quality, their carminative doses are: Powdered drug, 15 grains (1 gm.); oils, 5 minims (0.3 c.c.); waters, 1 dram (4 c.c.); spirits, 10–30 minims (0.7–2 c.c.); tinctures, 30 minims (2 c.c.); aromatic fluidextract, 30 minims (2 c.c.).

BITTERS

These are substances that are employed to give a bitter taste, the object of their administration being to improve the appetite. When the appetite is below normal, a strong stimulation of the taste-buds will often restore it; and substances with a bitter taste that is not otherwise disagreeable tend to act as stimulants to the taste-buds.

That appetite is important for digestion has been demonstrated by Pawlow and his followers. They discovered that the stomach of a hungry dog would secrete gastric juice if he saw or smelled food, even though there was no food in the stomach. They called this the "appetite" or "psychic" gastric juice. They also found that some foods would not digest at all,—for example, white of egg,—if they were put in the empty stomach without arousing the appetite, as through a fistula while the animal slept. That is, they were incapable, by direct action on the stomach-wall, of inducing the stomach to secrete. But Pawlow noted further that, on showing the dog food, the appetite juice would form and would act on the egg-albumin; and that the products of this primary digestion would then stimulate the stomach-wall and induce the secretion which continued the digestion. Hence the appetite juice is of great importance in starting

The *syrup of yerba santa*, dose, 1 dram (4 c.c.), has been much employed as an addition to bitter medicines, especially quinine. It lessens the appreciation of bitter taste, but in swallowing hardly acts rapidly enough to check the taste of a bitter substance mixed with it; in fact, to get the real anti-bitter effect, it is necessary to hold the yerba santa preparation in the mouth for several minutes before the bitter is taken. Yerba santa is itself bitter and very astrigent. It contains tannic acid in abundance, and it is largely by forming the insoluble tannate that it lessens the bitterness of quinine and other alkaloids.

CHARCOAL

Animal charcoal (carbo animalis) is prepared from bones, and 85 per cent. of it consists of mineral matter. It is called "bone-black." *Purified animal charcoal* is bone-black boiled with hydrochloric acid and washed thoroughly with water. It is almost pure carbon. **Wood charcoal** (carbo ligni) is prepared from soft wood; it is nearly pure carbon. Dose of charcoal, 15 grains (1 gm.).

Purified animal charcoal possesses the power, in a high degree, of absorbing organic colors, hence is used largely in pharmacy and the arts for decolorizing, as in the refining of sugar and petroleum. It has also a certain amount of power to remove certain resins, bitter principles, and alkaloids from their solutions, and Lebourdais has in this way recovered digitalin, colocynthin, strychnine, quinine, and other active principles. Owing to this property, it has been proposed as a remedy in mushroom poisoning, arsenic poisoning, strychnine poisoning, etc., ½ ounce (15 gm.) being the dose for each grain of strychnine salt swallowed. Unfortunately, this property of absorption cannot be depended upon. Wood-charcoal and bone-black are very inferior as absorbents.

In medicine, *wood-charcoal* has been used in flatulency because of its known power of absorbing gases. But when saturated with liquid, it loses this power of gas absorption, hence in fermenting stomach-contents is of little or no value. In the study of the stools it is much employed in timing the passage through the alimentary tract. A dose of 30 grains (2 gm.) given with a meal will color the stool resulting from that meal black or gray-black.

EMETICS

These are drugs employed to induce vomiting. To produce emesis requires the coördination of several mechanisms, the

contained methemoglobin; the bladder was filled with dark-brown urine.

Potassium chlorate mixed dry with sulphur, hypophosphites, and oxidizable organic matters, is likely to explode. In the form of tablets it has frequently caused fire on contact with sulphur matches.

The **vegetable astringents** contain either resins or tannic acid. The resinous astringents are *myrrh*, a tincture of which, diluted with water, is used for soft and bleeding gums, and *hydrastis*, whose tincture, diluted with water, is used locally in vaginitis and urethritis.

The tannic-acid astringents are: blackberry root (rubus), catechu, galls, gambir, geranium, kino, krameria, logwood (hematoxylon), oak-bark (quercus), rosa gallica, sumac fruit (rhus glabra), and witch-hazel bark (hamamelis).

Preparations and Doses.—*Extracts*—Logwood, 15 grains (1 gm.), krameria, 7½ grains (0.5 gm.).

Fluidextracts—Blackberry, geranium, krameria, oak, rose, sumac (rhois glabræ), witch-hazel (hamamelidis foliorum); dose, 15 minims (1 c.c.).

Tinctures—Kino and compound gambir, each, 5 per cent.; and galls and krameria, each, 20 per cent.; dose, 30 minims (2 c.c.).

Syrup of krameria, 45 per cent; dose, 1 dram (4 c.c.).

Troches of krameria, each, 1 grain (0.06 gm.).

TANNIC ACID OR TANNIN (Acidum Tannicum)

This substance is prepared from nutgalls. It is slowly but completely soluble in less than its own weight of water or alcohol, and, with the aid of heat, in its own weight of glycerin. It is used locally in 5 to 20 per cent. preparations, or internally in dose of 5 grains (0.3 gm.). The ointment, the glycerite, and styptic collodion are of 20 per cent. strength. The troches contain 1 grain (0.06 gm.) in each. Tannic acid is incompatible with alkaloidal salts, metallic salts, such as mercuric chloride, lime-water, gelatin, and protein. The precipitation of the gelatin and proteins of hides is "tanning," and changes the hides into leather. In like manner tannic acid renders insoluble the coatings of gelatin capsules and pills.

Its astringency depends upon its power to precipitate the proteins of the superficial cells, thus causing shrinking of the tissues and stoppage of secretion. It checks small hemorrhages, *i. e.*, is hemostatic or styptic, by coagulating the blood. In the stomach it precipitates the proteins of the food, but these redissolve in the gastric juice. Its effect on mucous membranes is to check secretion. Strasburger believes that the lessening of

and to give a brisk cathartic, the object being to clean out the intestines and leave the worm in an exposed condition. The dose is then administered, and is followed in four or five hours by a brisk, rapidly acting cathartic, such as castor oil or salts, to carry out the worm. Castor oil has been objected to on the ground that an oily medium will promote the absorption of the poison by the patient. This may be true if rapid evacuation of the bowels does not take place; but castor oil and its soap products hurry through the intestines and are not much absorbed unless catharsis fails. The different kinds of parasite require different kinds of treatment, as follows:

1. **The Pin- or Thread-worms** (*Oxyuris Vermicularis*).—These are tiny, thread-like organisms which live in great abundance in the colon or the adjoining portion of the ileum, chiefly in the mucus. As they do not cling to the intestinal wall, they are readily carried out by cathartics; or, as they are very vulnerable, may be attacked by destructive colon irrigations or enemata. Occasionally they penetrate the mucous membrane of the intestine or inhabit the appendix, and then they cannot be dislodged.

The cathartics mostly employed are calomel and castor oil. A number of substances are used for colon injection, viz., the infusion of quassia, lime-water, a solution of phenol, 0.25 per cent., a solution of quinine bisulphate, 1:2000, a solution of tannic acid or alum, 30 grains (2 gm.) in one pint (480 c.c.), and soap-suds containing ½ ounce of the oil of turpentine to a quart. The astringents are effective not only by shriveling the worms, but also by lessening the intestinal mucus in which the worms may lodge. The *Tænia nana*, which are tiny tape-worms, are sometimes taken for pin-worms.

2. **The Round-worms.**—1. The common round-worm, *Ascaris lumbricoides*, grows to a length of 6 to 12 inches or even more. They usually inhabit the small intestine, but may be found in the colon or stomach, and have even been known to stop up the common bile-duct. The author has had several patients who have vomited round-worms, and in two instances drew up a piece of round-worm through a stomach-tube. These must have been in the stomach. They may be the cause of intestinal hemorrhage. The remedies are:

Santonin (santoninum), a glucoside from santonica (Levant wormseed), dose, 2 grains (0.12 gm.) for an adult, and 1 grain (0.06 gm.) for a child of five years. The ½-grain (0.03 gm.) troches are official. Santonica, ½ dram (2 gm.), is sometimes taken as it is or in the form of an infusion. Santonin is highly toxic, and death has occurred from 5 grains (0.3 gm.) in an

(3 to 4 gm.) for an adult, given in 5-grain (0.3 gm.) capsules. Musgrave recommends thymol for irrigation in amebic colitis.

3. The **tape-worms** seen in America are mostly that of beef, *Tænia saginata;* that of fish, *Tænia bothriocephalus;* and the dwarf tape-worm, *Tænia nana.* The remedies are sometimes called teniacides and teniafuges. The favorite remedy is *oleoresin of aspidium* (male-fern), 1 dram (4 gm.) in capsules. Others are *cusso*, 1 dram (4 gm.) in infusion; *granatum* (pomegranate root bark), 2 drams (8 gm.) in infusion; *pepo* (pumpkin-seed), ½ ounce (15 gm.) in infusion; *kamala*, 1 dram (4 gm.) mixed with syrup; *oil of turpentine*, ½ ounce (15 c.c.), and *chloroform*, 1 dram (4 c.c.). *Pelletierine*, an alkaloid from granatum, in the form of the tannate, dose, 4 grains (0.25 gm.), and *amorphous filicic acid*, one of the constituents of male-fern, dose, 10 grains (0.7 gm.), are also employed. Power and Salway failed to find any anthelmintic properties in the constituents of pumpkin-seed.

Poisoning by aspidium, granatum, and kamala shows in gastro-intestinal irritation, with vomiting, purging, stupor, vertigo, muscular twitching, collapse, and perhaps irritation of the kidneys. There may be hemolysis with jaundice (Grawitz). We have several times seen severe gastro-enteric irritation with vertigo and prostration result from the hospital "Early-Bird" mixture. This consists of pumpkin-seed, 2 drams (8 gm.), cusso and granatum, each, 1 dram (4 gm.), made into an infusion, to which are added kamala, 1 dram (4 gm.), oleoresin of aspidium, 1 dram (4 gm.), glycerin, ½ ounce (15 c.c.), mucilage of acacia, ½ ounce (15 c.c.), and water to make the total amount 8 ounces (240 c.c.). After the usual preliminary starvation, this quantity is taken in two drafts two hours apart. The "early bird" usually gets the worm.

CATHARTICS

A cathartic is a measure designed to promote defecation. Such a remedy may be employed—(1) In cases of constipation; (2) for the removal of irritating or otherwise harmful material from the intestines, as in food-poisoning, intestinal putrefaction, and some forms of diarrhea; (3) for general depletion, as in plethoric or dropsical states, cerebral congestion, etc.

Constipation is a condition of insufficient frequency of defecation, or of insufficient quantity regardless of frequency, or of hardness and dryness of the feces. The usual number of stools in a day is one or two, but many people maintain health

is placed in a loop of intestine tied off without injury to the vessels (a Moreau's loop), the wall of the loop soon becomes congested and shows signs of inflammation, and the contents of the loop contain inflammatory products. Their cathartic action is often accompanied by violent cramps and abdominal soreness, and in this event may result in stools containing blood or serum-albumin. After the larger doses in man, if catharsis does not result in a reasonable time, the drugs accumulate in the cecum and colon, and may cause serious inflammation. In such case, too, they may be slowly absorbed and passed out by the kidneys, and these they irritate severely, even to the production of an acute nephritis.

The writer saw a case of hysteria which had been treated for obstinate constipation by the administration, in a period of twenty-four hours, of a seidlitz powder, three compound cathartic pills, 2 drams (8 gm.) of compound jalap powder, and 3 minims (0.2 c.c.) of croton oil. These resulted in no movement of the bowels until shortly after the last dose. Then there was a violent diarrhea, with blood in the stools, severe abdominal cramps, bloody urine, and later suppression of urine. The patient went into collapse and died in twenty-four hours. At postmortem examination there was an intense inflammation of the last few inches of the ileum and the whole cecum, in which region some brown drug was visible clinging to the wall of the bowel. There was also an acute hemorrhagic nephritis. The drastics had caused these lesions.

On Dr. Theodore Janeway's service at St. Luke's Hospital a girl of nineteen was admitted with similar but less severe poisoning from "bitter apple" (colocynth), given to her by a druggist. She had vomited six hours after the dose, and repeatedly for twenty-four hours, with almost constant diarrhea and a dull ache across the lower abdomen. She was admitted the following day to the hospital, the temperature being 99.8° F., the pulse 116, and the leukocytes 27,200, with 82.5 per cent. of polymorphonuclears. She still had the gastro-enteritis, and vomited twice after admission; but the kidneys were apparently unaffected, probably owing to the free diarrhea. The patient made an uneventful recovery in four days.

In poisoning, the immediate indications for treatment are: (1) To remove the poison by a saline cathartic or castor oil or by colon irrigation, and (2) to check collapse. After the immediate clearing out, bland oils or bismuth salts in large amounts may be given. The subsequent treatment is that for acute colitis, as by bland diet and bismuth salts by mouth, warm oil

ordinary drinking or washing water. Many bottled waters are not mineral waters. As obtained from the earth, they are *thermal* when they are distinctly warmer than the average surrounding temperature, otherwise *non-thermal;* some writers adopt 70° F. as the dividing line between these. Warm waters are those from 70° to 98.6° F.; hot waters are those above 98.6° F. They may be *sparkling* or *effervescent, i. e.*, impregnated with carbon dioxide, or *still, i. e.*, non-effervescent. They may be sulphurated, containing hydrogen sulphide gas. Their mineral constituents are sodium, potassium, lithium, magnesium, calcium, iron, aluminium, and arsenic, in the form of sulphates, nitrates, chlorides, bromides, iodides, borates, and silicates. In a number of the waters the percentage of the ingredients has been found quite variable at different seasons and in different years. The report of Haywood and Smith (1905), of the United States Bureau of Chemistry, on the "Mineral Waters of the United States," and that of Francina, on "European Waters," furnish valuable data.

A medicinal classification is not readily made because many waters contain more than one ingredient of importance. All are either—(1) *Alkaline, i. e.*, having an alkaline reaction; this comes from carbonates and bicarbonates, or in a few instances from borates and silicates. (2) *Saline*, containing chlorides, nitrates, or sulphates in excess. (3) *Alkaline saline*, combining the properties of the alkaline and the saline, or (4) *Acid*, in which there is free sulphuric or hydrochloric acid.

Any of these may contain one or other of the special elements, and are known as:

Sulphur waters—those containing sulphuretted hydrogen and other sulphides. They are usually from "red" or "white" sulphur springs, these names being obtained from the precipitation of sulphur. The red sulphur gets its color from iron. Examples are the waters of Richfield Springs or Sharon Springs.

Chalybeate or ferruginous waters—those which contain iron, usually in the form of the sulphate or bicarbonate, as Spa.

Arsenical waters—those which contain arsenic, as Levico and Bourboule.

Alum waters—those which contain aluminium salts. Rockbridge alum water contains 337 grains of aluminium sulphate per million and is astringent.

Bromine waters, *iodine waters*, etc.

Lithia waters—of these, Haywood and Crook say "lithium seldom or never occurs in waters in large enough quantities to be a predominating basic constituent." In their analyses, Buffalo and Londonderry Lithia Waters show only a trace, Otterburn

is to change its rhythmic projection of impulses, so that the heart-rate shows regularly alternating short phases of acceleration and slowing. That is, the rate rhythmically waxes and wanes, whether the total rate is slowed or not. This is also the effect of vagus stimulation, and it is abolished by atropine. It is known as sinus arhythmia or phasic arhythmia. During forced inspiration and expiration this arhythmia is physiologic, and may be observed in most people, the phases corresponding with the phases of respiration. But when it results from digitalis it sometimes has no relation to the respiratory rhythm; it is then an indication of beginning poisoning.

Summary.—Through the sinus node the digitalis effects are either slowing of the rate or sinus arhythmia or both, or possibly momentary standstill. They result from vagus stimulation.

B. The Cardiac Muscle.—The striking properties of the heart muscle, as viewed pharmacologically, are *tonicity*, *contractility*, and *irritability* (excitability). *Tonicity* of muscle is its property of maintaining, during its resting period, a state of partial contraction or incomplete relaxation, *i. e.*, a state of tone, which keeps it in readiness to respond promptly when a stimulus comes. In a hollow organ like the heart the tone gives it resistance to a bursting pressure during the period when the organ is not actively contracting. It is measured by the degree of relaxation in diastole. *Contractility* is the power of contraction in systole. It is measured by the size of the heart at the end of systole. Tonicity differs from contractility, which has to do with the active contraction, and from irritability, which deals with sensitiveness to stimuli.

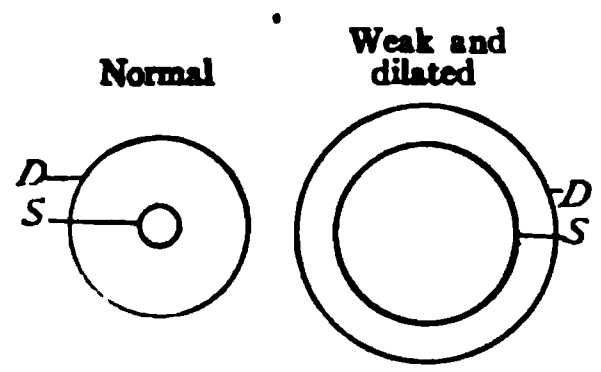

Fig. 7.—*D*, Capacity at end of diastole; *S*, capacity at end of systole.

1. *Contractility and Tonicity.*—In a heart whose contractility and tonicity are below the normal, the ventricular chambers are dilated and weak, so that in diastole the muscle is stretched beyond the normal by the venous inflow, and in systole contracts feebly. The result is a decreased output of blood.

If we take two concentric spheres and let one represent the capacity of the heart during the resting period of diastole, and the other the capacity at the end of systole, we might represent the normal and the weak heart, as in the illustration, the diminished excursion of the muscle lowering the output.

Digitalis, by increasing the tone and contractility, tends to

rmal, and so increases the out-
ing this effect may be deter-
ose of atropine to a laboratory
s, and a dose of apocodeine to
nfluences through the nervous
digitalis still results in striking
nicity. It must, therefore, stimu-
these effects with decided force
to some extent in therapeutics.
ts muscular wall is normally much
proportionally as the left. In
ventricle, through compensation,
the employment of digitalis may
ally if the heart shows "normal
sis below.)
e also strengthened and toned, a
in a weak, dilated heart. For
coincidentally with the ventricle, or

ventricular extrasystole." *As*, Auricular sys-
the ventricle beats spontaneously This
ed, during which the regular auricular im-
e does not beat until the next auricular im-
roughout

bulge into the auricle during systole
ency, *i. e.*, a leakage backward. As
al ventricular contraction begins in

ity is the susceptibility to stimuli.
mine the rate of the heart, for the
sinus node. But an increase of irri-
tends to result in spontaneous mus-
not have their origin in the sinus node.
harmful. They may be produced by

tability may show in auricular or
s, in paroxysms of tachycardia, in
ventricular fibrillation. In some
alternations of premature beats,
d auricular fibrillation.

improvement in the circulation under digitalis cannot be fully judged by estimations of the arterial pressure.

The Pulmonary Arteries.—These tend to be contracted, though the extent or the significance of this effect is not known.

The Cutaneous Arteries.—The arteries of the face and neck tend to dilate and cause flushing. This seems to have no appreciable effect on the general arterial pressure, and is not of importance. It is presumably from a central rather than a peripheral action.

The Veins.—The effect of digitalis upon the walls of the veins is similar to that upon the arteries, though it is probably of no therapeutic significance.

Kidneys.—The cardiac effects of digitalis extend further and may be seen in the action of the kidneys. With an unobstructed ureter a normal kidney will secrete more urine if more blood flows through it. And the factors which affect the amount of blood flowing through the kidney are: the general arterial pressure, the degree of contraction of the kidney arteries, and the freedom of the venous outflow. Venous back pressure, however slight, or contraction of the kidney arterioles, or a fall in general arterial pressure, will have a tendency to lessen the amount of urine; while a reversal of these conditions favors an increase in the amount of urine.

As measured by the oncometer, the normal kidney of an animal shrinks after a laboratory (poisonous) dose of digitalis. This diminution in size is synchronous with the vasoconstriction in other parts of the body and with the rise in arterial pressure, hence it may be assumed that the kidney arterioles, in the same way as the other arterioles, are constricted by poisonous amounts of digitalis. But in human therapeutics, as we have seen, there are presumably no essential constriction of arteries and no striking rise in arterial pressure. It is a fact also that the digitalis principles apparently reach the kidney in such diluted form that, in therapeutic amounts, they have no direct irritant action upon the kidney structures. Therefore, the output of urine in persons with normal circulation is unaffected.

Hedinger (1910) gave digipuratum and digalen to rabbits intravenously, and when the kidneys were normal, obtained a slight increase in the volume of the kidney, but a scarcely perceptible diuresis. In the early stages of tubular nephritis he obtained increase in kidney volume (dilatation of the arterioles) and a greater diuresis. In more severe tubular nephritis and in vascular nephritis there was no diuresis. Jonnescu and Loewi obtained a small diuretic effect from digitalis in normal animals.

They believed that the drug could cause a local dilatation of the kidney arterioles, as do most diuretics.

In man, the local action, if any, is a negligible one, and not at all to be compared with that of theobromine. The maximum increase in the daily urination in health as noted after digitalis is about 200 c.c., and usually there is no essential change.

But in cases with low general arterial pressure and venous engorgement, *i. e.*, in persons with failing circulation, there is regularly very little urine formed; and in these cases the administration of digitalis may be followed by a great increase of the kidney excretion. In response to digitalis, in cases with failure of the circulation we have seen a urine output of 15 or 20 ounces a day change to one of 100 or 200 ounces, at least for two or three days. So *digitalis is diuretic only when it brings about improvement in a poor circulation.*

Digitalis diuresis is dependent upon—(*a*) improvement in the general circulation, through which accumulated tissue fluid passes into the blood to make hydremic plethora, and (*b*) improvement in the kidney circulation. It is not due to a direct action of the drug upon the kidney cells. Consequently the marked diuresis lasts only until the excess of fluid in the body brought about by venous stagnation is removed.

The urine is very dilute and poorly colored on account of the high proportion of water, but, at least for the first few days, contains an actual increase in the total solids, and particularly in the salts and urea. It is probable that this is due to the washing out of stored-up material.

In severe poisoning, digitalis may result in the appearance of albumin and blood in the urine. This is due either to a remote local irritant action resulting in nephritis, or to excessive vasoconstriction. Either of these may also be a cause of suppression of the urine. (*Suppression* is a term to be distinguished from retention. It signifies failure of the kidneys to secrete urine, while *retention* applies to the bladder, signifying failure of the bladder to empty itself.)

Venous Engorgement—Edema and Dropsy.—In cases with failing circulation there is regularly some degree of venous engorgement, *i. e.*, venous back pressure. And venous engorgement means:

1. Increased general capillary transudation. This results in increased formation of tissue fluid.

2. Obstruction to the flow of lymph; because the lymphatics empty into the veins. This checks the removal of tissue fluid.

3. Lessened capillary absorption of tissue fluid, because of sluggish blood-flow.

PLATE I

a b c

d *e*

These two figures show a continuous tracing taken from a dog following an intravenous injection of 1 mg. of strophanthin per kilo. Upper tracing, auricle; middle tracing, ventricle; lower tracing, arterial pressure. *a*, Strophanthin injected; *b*, second stage begins; *c*, rate of drum increased; *d*, abrupt change to third stage; *e*, auricle fibrillating, ventricle fibrillating, death. (Tracing made by Dr. C. C. Lieb.)

But the death occurs in spite of artificial respiration, and is due to failure of the circulation from ventricular fibrillation, which in mammals usually takes the place of the continued systole of cold-blooded animals.

We have recently had reported to us one such death from the intravenous administration of digitalis in a human being, and several following the intravenous use of $\frac{1}{65}$ grain (1 mg.) of strophanthin, death resulting in from three minutes to about an hour. Serious symptoms have also been reported from $\frac{1}{30}$ grain of digitoxin. These deaths have usually occurred in patients who had been taking digitalis for several days previously.

3. *Cumulative Poisoning.*—This comes from the use of the drug in medicine. The signs of overdosage in the medicinal administration of digitalis should be recognized as soon as possible, for such poisoning is common in hospital and private practice, and its manifestations are not infrequently misinterpreted as symptoms of the heart disease. But there are a number of cases in which we may be unable to say with certainty that digitalis is the cause, until we note the disappearance of the manifestation shortly after the digitalis is stopped, and its reappearance under further administration of the drug.

MANIFESTATIONS OF OVERDOSAGE OF DIGITALIS

I. SUBJECTIVE MANIFESTATIONS:
- *a.* Loss of appetite, nausea, vomiting, diarrhea.
- *b.* Oppression about heart, palpitation, tachycardia, consciousness of premature or skipped beats.
- *c.* Headache.

II. OBJECTIVE MANIFESTATIONS:
- *a. Effect on sinus node*—
  1. Excessive slowing.
  2. Sinus arhythmia { Exaggerated respiratory. / Non-respiratory. }
- *b. Effect on a-v bundle* { Prolonged auriculoventricular interval (incipient block). / Partial or complete block (with or without bradycardia). }
- *c. Effect on muscle*— Overexcitability {
  1. Premature beats (extrasystoles).
  2. Paroxysmal tachycardia.
  3. Nodal and retrograde rhythms.
  4. Auricular fibrillation.
  5. Ventricular fibrillation.

heat. By prolonged boiling it is quite changed. On long standing, or if diluted, it deteriorates, slowly changing to a reddish color and eventually precipitating. It keeps better when it contains a slight excess of hydrochloric acid. When a precipitate is present, the solution should be discarded. Tablets of the hydrochloride, the pure alkaloid, and the tartrate are also obtainable. A synthetic substitute, suprarenin, has about half the strength (Schultz). It is dioxyphenyl-ethanol-methylamine chloride.

The dried suprarenal glands of the sheep and ox, freed from fat, and cleaned, dried, and powdered, are official under the title "Glandulæ Suprarenales Siccæ." This dried gland is about six times as strong as the fresh gland, and is used either in tablet form or in a mixture with water. The latter must be freshly prepared, as it does not keep.

Preparations and Doses.—The dose varies according to the method of administration and the effect desired.

Dried Suprarenal Gland.—Dose, 4 grains (0.25 gm.) by mouth.

Solution of epinephrine chloride, 1 : 1000, used hypodermatically in asthma, urticaria, etc., 15 minims (1 c.c.); used intravenously, 2 minims (0.12 c.c.); or in shock, 30 minims (2 c.c.) added to saline and very slowly administered.

Reid Hunt, and also Sollmann and Brown, in 1906, called attention to the great variability and poor keeping qualities of preparations of adrenaline chloride. Schultz (1910) established a definite standard for assay, and on testing the blood-pressure-raising power of the several commercial preparations as compared with pure solutions of epinephrine, found them to be of variable efficiency.

Pharmacology.—General Action.—Epinephrine is a stimulant of sympathetic nerve-endings or their myoneural junctions. As Langley puts it, "the effects of adrenaline upon any tissue are such as follow excitation of the sympathetic nerve which supplies the tissue." The effects, so far as muscular activity is concerned, depend upon the degree of contraction already existing. Thus, with greatly relaxed arteries, the proportional response is greater than with arteries in normal contraction; and with contracted bronchi the relaxation is greater than in normal bronchi. Hence a dose which will constrict relaxed arteries may not affect the bronchi; and a dose which will relax contracted bronchi may not constrict normal arteries.

Skin and Mucous Membranes.—It has no effect on the unbroken skin, but when applied to cuts, open wounds, ulcers, or any mucous membranes which can be reached (namely, those of

a *b*

Fig. 25.—Pituitary extract. At *a*, that of one manufacturer; at *b*, that of another, in each case 0.1 c.c. per kilo intravenously. The dose at *b* stopped the auricle (upper tracing), lowered the tone and contractility of the ventricle (middle tracing), and caused a moderate but fairly prolonged rise of arterial pressure (lower tracing), with slowing of the pulse from 162 to about 84. (Tracing made by Dr. C. C. Lieb.)

of epinephrine. Occasionally the action lasts as much as half an hour.

But there is a marked difference in the site of action from that of epinephrine, for the slowing of the heart takes place after atropine, and is, therefore, a muscular and not a vagus effect; and Wiggers, and also McCord, have shown, by perfusion experiments, that after apocodeine or ergotoxin, while epinephrine has no vasoconstrictor action at all, pituitary extract constricts the vessels as much as it did before. Also, pituitary constricts the coronary, pulmonary, and cerebral arteries. Hence it must act by stimulating the muscles of the arteries and not the vasoconstrictor nerve-endings. Wiggers recommends it in pulmonary hemorrhage.

With isolated arteries the doses may be repeated indefinitely, and vasoconstriction is always the result. But McCord reports that, in the intact animal, after several repetitions of the dose, the arterial pressure falls. This fall has been shown by McCord to be due neither to lessened output of the heart nor to a central dilating influence, but to the conversion of the constrictor action into a peripheral dilator effect on the wall of the vessels. This action results when the pituitary reaches a certain concentration in the blood. But Lieb and Bastedo failed to get any dilator effect from nine successive large doses.

Splanchnic Organs.—In perfusing the isolated kidney in an oncometer, the addition of pituitary regularly results in a shrinkage in size and a lessened venous output; but with the kidney of an intact animal, the volume is increased (sometimes after preliminary shrinkage), and there is increased venous output and increased urination (Wiggers, 1911). Sollmann and Pilcher have shown that, so far as the vessels of the spleen are concerned, there is a central vasodilator action, and McCord has been able to demonstrate the same action on the kidney vessels. The intestinal muscles are also stimulated and peristalsis increased.

Uterus.—The stimulating action on smooth muscle extends to the uterus, and in dose of 15 minims (1 c.c.) the drug has recently been given by deep intramuscular injection for menorrhagia, subinvolution, and, at the time of labor, for uterine inertia. Cases of dangerous constriction from this have been reported. Hauch and Meyer (1912) warn against its use in cases with high arterial tension. Brammer noted such violent contractions of the uterus in one case that he had to administer chloroform. Schaefer says it also increases the secretion of milk.

Internal Secretions.—In hyperthyroidism, pituitary has at times seemed to lessen the excessive thyroid secretion, with disappearance of the acute symptoms. It tends to inhibit the flow of pancreatic juice (Wiggers).

failure, where stimulus production in the heart threatens to fail, camphor is undoubtedly to be considered a heart stimulant. For in perfusion camphor will overcome the fibrillation of the auricle which is caused by chloroform and other poisons, and even that from electric stimulation, and it will prevent the excessive slowing and weakening brought on by chloral hydrate." Heinz says practically the same.

In one case of septicemia in which the author injected 5 grains (0.3 gm.) of camphor in oil hypodermatically three times a day for two days there occurred, on three occasions, for about two hours after the dose, a distinct weakening of the heart, with depression of the respiration and Cheyne-Stokes breathing.

Heard and Brooks (1913) tested camphor on human beings. In 5 cases with normal circulation a hypodermatic of camphor, 20 grains (1.3 gm.) in oil, showed in four no change in the circulation, and in the other one a fall of 17 mm. in systolic and 25 mm. in diastolic pressure. In 9 cases with auricular fibrillation and other cardiovascular conditions there was no change, except in 2 of them a very slight rise in pressure. Their observations were made for from forty to two hundred and seventy minutes after the injection. The only rises in pressure were in cases with great mental excitement, and in these, on a second test, there was no rise. Even as much as 50 grains (3.3 gm.) failed to produce any definite effects, either desirable or toxic. In perfusing a cat's isolated heart, camphor in saturated solution was without effect on the normal heart, but in 2 instances checked experimental fibrillation.

We do not think it should be used as a heart stimulant at all, except as a single dose in emergency. Even then it is entirely unreliable.

Respiratory Organs.—As with other carminatives, there is a reflex stimulation from the stomach or mouth. Systemically, after large doses, there is some stimulation of the respiratory center. It is thought that some of the drug is eliminated in the bronchial mucus; but if this is so, the dose of 2 grains or thereabouts is too small for any effective remote local action.

Cerebrum.—Given by mouth, camphor tends to lessen hysteric excitement and nervous instability. All strong carminatives do this to some extent, but camphor, valerian, and a few other drugs seem to exert an antihysteric influence quite out of proportion to their value as carminatives. This probably is the effect of stimulation of the higher controlling centers of the brain (those governing reason, self-control, will, etc.). That camphor is a cerebral stimulant is shown by increased intellectuality and by the appearance, after excessive doses, of de-

lowed undiluted, causes great local irritation and inflammation of mouth, throat, esophagus, and stomach. There may be vomiting. The inflammation may go on to ulceration or general sloughing; and, if the patient recovers, may leave cicatricial constrictions which will give trouble in after-life. If the burns are very extensive, death may result from shock. The ammonia fumes may get into the larynx and produce edema of the glottis. *Treatment:* In the mouth or stomach, the poison may be neutralized by mild acids, such as vinegar or lemon-juice; the pain and inflammation may be lessened by bland oils or fats, such as olive or linseed oil, lard or butter, or by the white of egg, milk, or demulcent mucilaginous drinks.

2. *From Inhalation.*—Strong ammonia fumes inhaled, as from the escape of the gas in ice-plants, or when the liquid is swallowed, may cause swelling and inflammation of the larynx and bronchi, and through edema or spasm of the glottis may cause asphyxia and death. The *treatment* is to give plenty of air or inhalations of oxygen. If the glottis is closed so as to prevent breathing, intubation or tracheotomy should be performed. If there is edema of the glottis, the tissues should be cut at once to relieve the swelling.

Effects After Absorption.—If the poison is absorbed, there may be strychnine-like convulsions, collapse, coma, and asphyxia, death being due to paralysis of the respiratory center or to the convulsive interference with breathing. The treatment is artificial respiration, oxygen, absolute repose, external heat, and other treatment for collapse.

Therapeutics and Administration.—1. As a *counterirritant*—ammonia liniment or ammonia water. As a blistering-agent to the gums—ammonia water.

2. As a *rapid reflex circulatory and respiratory stimulant* in fainting or feelings of faintness—ammonia gas inhaled from ammonia water or smelling salts; or the aromatic spirit of ammonia, taken by mouth. Smelling salts are mostly made of cakes of ammonium carbonate covered with the spirit of ammonia containing aromatic oils, such as the oil of lavender.

3. As an *antacid carminative* in digestive disturbances and headache, and as a morning "pick-me-up" after a debauch—the aromatic spirit.

4. As an *expectorant* to fluidify thick and tenacious mucus of the respiratory tract—the carbonate.

Contraindication.—Urea retention, as in nephritis and uremia.

this action is so ephemeral that it probably has very little influence on the blood-stream.

Crile found, further, that the dilution of the blood does not prevent the action of circulatory stimulants; that if vasoconstrictor stimulants were administered at the same time as the saline, the arterial pressure could be raised above normal for a time; but that, when the splanchnic arteries were excluded, the dilution of the blood increased so rapidly with the progress of the infusion that edema set in very quickly, even though the arterial pressure was not essentially raised. This indicates that if, by a strong vasoconstrictor, such as epinephrine, dilatation of the splanchnic arteries is prevented, the chances of edema are increased. Hence in intravenous infusion, since the liquid must pass to the right heart and to the lungs first, pulmonary edema is favored; and especially is this the case if at the same time there is marked back pressure on the left heart from constriction of the peripheral arterioles. Therefore, as might be expected, pulmonary edema is especially readily brought about by a combination of saline infusion and epinephrine.

Summary.—When the volume of the blood has not been reduced, saline infusion to raise arterial pressure is almost useless, and by producing edema, may have serious consequences. If used as a medium for the administration of drugs, it should be employed in small quantity, and slowly introduced. By transfusion of blood, on the contrary, it has been found possible to raise arterial pressure away above the normal, and to maintain it there for some little time.

When the Volume of the Blood is Notably Below Normal; as After a Large Hemorrhage.—From 25 to 50 per cent. of an animal's blood may be removed and replaced with saline without serious results (Levin). Crile noted that after a moderate hemorrhage a saline infusion would increase the volume of the blood so that normal arterial pressure would be maintained for a considerable period. He found also that the blood has a shorter coagulation time, the saline thus favoring the cessation of the hemorrhage. So saline infusions are valuable to replace lost blood, and may be used with advantage whether the bleeding has stopped or not.

A few further observations of Crile on the effects of infusions are worth mentioning: *The temperature of the infusion*, if within reasonable limits, makes almost no difference, either in the temperature of the patient or in the heart-beat. The *rate of flow* makes no difference in the extent of the effect on arterial pressure. The *effect on respiration* is an increase in frequency and depth; but "from greater than safe amounts the breathing becomes

what leaves the liver is the chloride, and ammonia poisoning does not result.

Therapeutics.—For *acute pharyngitis* the troches or tablets may be dissolved in the mouth—a favorite remedy of the laity. Thus employed, the chloride is at first stimulating and astringent, so that it causes a drawing-up of the relaxed mucous membrane, with removal of its edematous state; it also promotes the flow of saliva, so may relieve congestion and dryness of the throat. In *laryngitis* or *bronchitis* the drug is occasionally inhaled as vapor, the vapor being formed at the moment required by the admixture of ammonia and hydrochloric acid gases in a special apparatus. But its most frequent employment is in cough mixtures, to increase the flow of mucus in the dry stages of nasal, throat, and bronchial inflammations, *i. e.*, when the congestion is great without mucous flow, or when the mucus is thick and tenacious.

2. Ammonium Acetate

The acetate, $NH_4C_2H_3O_2$, is an unstable salt, and on this account is prepared in solution when required. There are two official preparations—the solution of ammonium acetate (liquor ammonii acetatis; spirit of Mindererus), and the solution of iron and ammonium acetate (liquor ferri et ammonii acetatis; Basham's mixture), the dose of each of which is 2 drams (8 c.c.). The *solution of ammonium acetate* should be freshly prepared, and should contain CO_2 gas. It is a palatable, slightly salty preparation, is quickly absorbed, and is changed to urea in the liver, the urea promoting the flow of urine. It may also have a tendency to increase the sweat. It is employed as a refreshing but weakly acting diaphoretic and diuretic in fevers, especially those of children. *Basham's mixture* is a palatable iron preparation. As it contains free acid, it should be administered well diluted and through a tube, to protect the teeth. It is employed in anemic conditions for its iron, and in functional albuminuria or chronic nephritis for both its iron and its ammonium acetate.

3. The other official salts of ammonium are the bromide, iodide, benzoate, salicylate, and valerate. In these the effect of the ammonium radicle is overshadowed by the relatively more potent acid radicle, so that these salts, except in large doses, have practically the action of the potassium and sodium salts of the same acids. They belong, pharmacologically, with the groups of bromides, iodides, salicylates, etc.

Mechanical Measures for Raising Arterial Pressure

In hemorrhage or collapse, the immediate indication is to restore the circulation of the brain centers, particularly of the

vasoconstrictor and respiratory; so mechanical measures, to increase the blood of the trunk, such as raising the feet and lowering the head, or tightly bandaging the limbs, toes, or fingers upward, are valuable measures. By this latter method the blood-pressure may sometimes be raised 30 or 40 millimeters of mercury, and the bandages may be kept on for half an hour without harm to the limbs.

For use in shock Crile has devised a pneumatic suit, by which the surface pressure on the body may be increased or reduced at will. By it he has raised the arterial pressure as much as 75 mm., and maintained the rise for some time. To accomplish the same purpose, Meltzer recommends bandaging the abdomen and placing weights upon it.

MEASURES FOR INCREASING THE VOLUME OF THE BLOOD IN THE ARTERIES

These are—(1) The transfusion of blood; and (2) the administration of saline solution (by intravenous infusion, by hypodermoclysis, or by rectal injection).

Transfusion is the transmission of blood from an artery of one person to the vein or artery of another. It requires careful technic, involves the willingness of a second person to contribute blood, and is not free from danger. The dangers are—(1) Clotting (2) the transmission of disease, such as syphilis, (3) the collapse of the donor of the blood, and (4) hemolysis. Before transfusion the blood of the donor should be tested with that of the patient for fear of hemolysis. This is especially likely to occur in infants or in the presence of a malignant tumor (Crile). By recent improved methods the clotting and technical difficulties have been much reduced, so that transfusion, which was at one time abandoned, has again come into general use. The artery of the donor is usually connected with a vein of the recipient by some apparatus, and the blood allowed to flow gently for fifteen or twenty minutes, or until the donor begins to show the effects of loss of blood. In some cases transfusion into an artery brings a more prompt response than into a vein. For in transfusion into a vein the transfused blood may merely increase the volume of the already excessive venous blood, and in any case must pass to the right heart and through the pulmonary circulation before the left heart can act upon it; while by transfusion into an artery the new blood, owing to the increased peripheral resistance, stimulates the heart and invigorates the coronary circulation.

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aconite, beginning with 5 minims every two hours, then 10 minims, then 15. Although the dose was given for several days in many cases, not the slightest effect could be detected. Then, at Cushny's suggestion, he got Price to try aconitine in cases of auricular fibrillation in which digitalis proved effective, and in cases of rapid heart due to fever and other causes. Price carefully pushed the drug until the patient felt tingling of the tongue and skin, but in not a single instance did he get any evidence of a reaction on the heart or blood-vessels.

And Rudolf and Cole (1912), in tests on 55 patients with and without fever, failed to get any change in the pulse-rate. They gave as much as 4½ minims of the B. P. tincture, equivalent to 2¼ minims (0.14 c.c.) of the U. S. P. tincture, every ten to fifteen minutes for 8 to 10 doses.

From therapeutic amounts there is no depression of any part of the vasoconstrictor mechanism; and the drug lowers arterial pressure, if at all, by pure cardiac depression and not by dilatation of the arteries.

Respiratory.—From moderate doses there is stimulation of the respiratory center, with increased depth and frequency of respiration; but from doses beyond therapeutic there is early depression of the center, with slowing of the respiration, labored breathing, and lessening of the intake of air. In poisoning there may be also some stimulation of the sensory vagus endings in the lungs (for the accessory respiratory muscles contract vigorously), and a stimulation of the bronchoconstrictor nerve-endings, the result being bronchial spasm (Dixon). Death takes place from asphyxia due to paralysis of the respiratory center. If artificial respiration is maintained, the heart will continue to beat for some time after the respiratory center fails.

Cerebrum.—This is the last part of the nervous system to be affected, and consciousness is retained until the final stages of poisoning. The mind becomes dulled only when the patient passes into collapse.

Medulla.—The *vagus* center is stimulated, as already indicated; the *vasoconstrictor* center is stimulated by poisonous doses, but this stimulation soon passes into depression; the *respiratory center* is at first stimulated but very soon depressed, and through its paralysis death is produced. The *vomiting center* may be stimulated; the *heat-regulating center* may be affected so that temperature in fever is lowered. Convulsions may occur in the poisoning, and are due either to asphyxia or to stimulation of the reflex centers of medulla and spinal cord.

Peripheral Nerves.—The peripheral ends of the sensory and secretory nerves we have already spoken of. They are strongly

In human cases with systolic pressure above 200 mm. Hg the author has found that after 5 minims of amyl nitrite the change in pressure varies considerably. It might drop as much as 70 mm., to rise again almost to the original height in about five minutes. But so marked a fall in pressure is unusual, the change being mostly between 20 and 40 mm. In some of these high-pressure cases the response is very little, and in a few cases there is actually a rise in pressure of 10 to 20 mm. The action of amyl nitrite is too fleeting for use except in emergencies.

Nitroglycerin is given by mouth or hypodermatically, and in either case is almost instantly absorbed. The fall in pressure begins in one-half to three minutes, reaches its maximum in five to fifteen minutes, and disappears in one-half to one hour. In conditions of general arteriosclerosis the effect sometimes lasts several hours, and sometimes there is no change in pressure at all.

Sodium nitrite is given by mouth, and is less rapidly absorbed. It has been reported by G. A. Gibson and others as less effective than nitroglycerin, but recently several investigators (Matthews, and Wallace and Ringer, and Lawrence) have found it just as active as the other preparations, though slower in its action. Its effects come on in five to thirty minutes, reach their maximum in twenty to eighty minutes, and are completely over in one to two hours. In solution the nitrite changes to nitrate on exposure to air, and this may account for the adverse clinical reports.

Erythrol tetranitrate is administered by mouth, and is likely to be more slowly absorbed and more slowly decomposed by the blood. As a consequence, its effects are more gradual in their development. The drop in pressure begins in five to thirty minutes, reaches its maximum one-half to two hours later, and disappears in two to five hours.

Mannitol hexanitrate has an effect about the same as that of erythrol.

Wallace and Ringer found that with any member of the series the greater the dose, the greater was the fall in pressure. In one of their cases $\frac{1}{80}$ grain of nitroglycerin reduced the pressure from 210 to 60 mm. Hg in ten minutes, the pressure rebounding to 168 mm. in four minutes, and reaching its original figure in fifty minutes. In another patient sodium nitrite caused the pressure to fall from 210 to 100 mm. In cases with high arterial pressure the author has never secured such striking results, even from the administration of $\frac{1}{50}$ grain of nitroglycerine hypodermatically every two minutes for five doses.

Blood.—After enormous doses the hemoglobin is reduced and its power of liberating oxygen lessened by the formation of methemoglobin and nitric oxide hemoglobin. But in the thera-

ranged in a triradiate manner, so that its bite consists of three short deep gashes radiating from a common center. To insure that the bite shall be at the desired spot, the leech is placed inside a glass tube or over a hole in a piece of paper, the mouth of the tube or the hole in the paper being placed over the spot to be bitten. If the leech does not take hold, the skin may be pricked or a drop of blood or milk placed upon it, or the leech may be put in very cold water for a minute or two to arouse it.

The effect of the leech is that of wet-cupping, more or less blood being extracted. As the mouth of the leech secretes a substance (hirudin) which prevents the coagulation of the blood, the bleeding may continue for a long time after the animal is removed. Indeed, it may be necessary to employ something to stop the bleeding, *e. g.*, adrenaline. The leech may be removed easily by squeezing its head or by placing salt upon it. The Swedish leeches are considered the best, as they extract about half an ounce of blood, while the American leeches extract only 1 or 2 drams.

There are decided disadvantages in the use of leeches, viz.: 1. They may not be clean; in any case, they cannot be aseptic. 2. They may wander and get into one of the body orifices—*e. g.*, the ear, nose, vagina, etc. 3. They remove an uncertain quantity of blood.

On these accounts the *artificial leech* is sometimes employed. It consists of a syringe with a cup-like nozzle and a graduated barrel with which slow suction is made over a cut in the skin. It is merely a process of wet-cupping with a graduated syringe.

Hirudin is employed in laboratory work to prevent coagulation of the blood, the small amount of 0.02 gm. ($\frac{1}{3}$ grain) being sufficient to keep 1000 c.c. of blood fluid for a considerable time. It does not alter the viscosity of the blood, but if used in too large quantities, may cause agglutination and sedimentation of the corpuscles (Bence).

SHOCK AND COLLAPSE

Following severe trauma or a surgical operation, there develops at times a condition of pronounced muscular relaxation, with rapid, weak heart, low blood-pressure, and depressed respiration. There is a similar state into which a patient may pass as the result of severe disease or loss of blood. But whether the effects when produced by a severe infection acting steadily for days are the same as those from trauma, or are produced in the same manner, are questions not yet decided. And, further, there is not by any means an agreement as to just what does

anesthesia, some not. Those without the preliminary spinal anesthesia showed a short rise in arterial pressure for five to ten minutes, then a rapid fall in pressure, and death in twenty-five minutes (average). In the dogs with spinal anesthesia there was no change in the arterial pressure for one hour, then a gradual fall until death, presumably as the cocaine effect was wearing off.

2. Dogs were completely anesthetized with ether, and then had their hind legs crushed to a pulp by repeated blows of the blunt side of an ax. After twenty minutes, given for shock to develop, both hind legs were amputated at the knee. A preliminary ligation of the femoral arteries was done to exclude the effects of hemorrhage. In all the dogs without spinal analgesia there was marked shock, and 2 out of 7 dogs died during or immediately after the amputation. The dogs which had a spinal injection before the amputation were all in good condition after the amputation, and remained so until the cocaine effect had worn off.

Porter states that the vasoconstrictor center is not exhausted in shock, as it responds in the usual way to stimuli through sensory nerves. But in well-developed shock the center is evidently not easily influenced, or else the usual pressor influences are changed to depressor. (See Strychnine.) And it has been suggested that in shock the constrictor synapses are easily paralyzed, so that the usual vasoconstrictor stimuli become vasodilator.

No matter what the underlying factors involved, Hill figures that the condition of shock or collapse is associated with cessation of the reflexes which maintain the body in a state of vascular tone and muscular activity.

Respiratory paralysis must be considered with collapse. It may be due to direct or reflex depression of the center, or to the failure of the circulation to bring the center sufficient CO_2 for its stimulation. The symptoms are those of asphyxia, resulting in death unless artificial respiration is maintained. If the heart action remains good, artificial respiration may often be continued until the center regains its activity.

The Symptoms and Treatment of Collapse and Shock.—Whatever the cause or the condition, therapeutically there are about three distinct degrees:

1. *Mild and transitory collapse* is the result of a momentary suspension of the cerebral circulation, as a reflex effect from sudden emotional or psychic influences, or from a drug like amyl nitrite or nitroglycerin, or from momentary ventricular stoppage, as in heart-block. It is probably due to anemia of the brain, caused by the dilatation of the splanchnic arterioles, and this

(illuminating gas), transfusion may follow a preliminary venesection (Crile).

REMEDIES WHOSE CHIEF ACTION IS UPON THE CENTRAL NERVOUS SYSTEM

a. The stimulants.

b. The depressants.

Those which stimulate the central nervous system are: caffeine, strychnine, atropine, and cocaine.

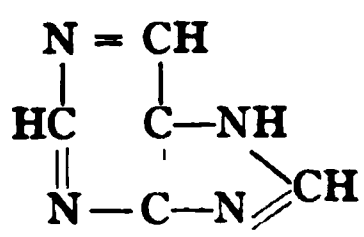
CENTRAL NERVOUS STIMULANTS

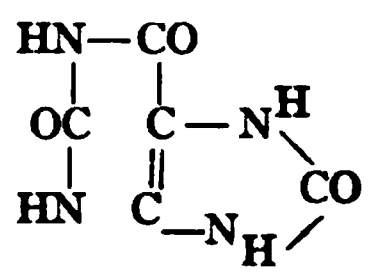
THE CAFFEINE GROUP

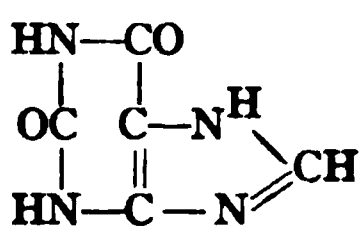
This includes the three alkaloids, caffeine, theobromine, and theophylline, caffeine being chemically a trimethyl xanthine, and the other two, dimethyl xanthines. They are purin bodies, are closely related to uric acid, and are but feebly basic, *i. e.*, have little power to form salts.

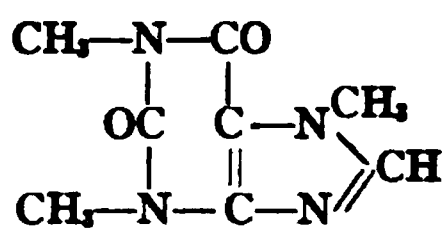
There are three classes of purins:

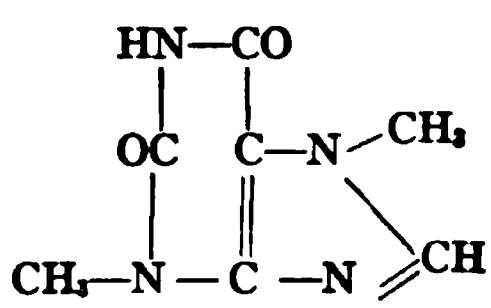
1. The *oxypurins*, which include hypoxanthine, xanthine, and uric acid (trioxypurin or oxyxanthine).
2. The *aminopurins*, which include adenin and guanin.
3. The *methyloxypurins*, which include this caffeine group.

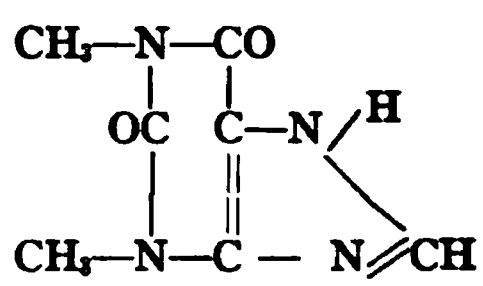

Purin, $C_5H_4N_4$


Uric acid, $C_5H_4N_4O_3$


Xanthine, $C_5H_4N_4O_2$


Caffeine, trimethyl xanthine.


Theobromine.


Theophylline.

By these formulæ the purin nature of the drugs of this group is evident, as also their close relation to uric acid.

CAFFEINE

Trimethylxanthine, or *caffeine*, is a feebly basic alkaloidal body usually prepared from damaged tea-leaves. It is found in plants growing in different parts of the world, and of no close botanic relationship; and the finding out, by the inhabitants of these different countries, of the value of their particular plant in making a stimulating beverage, and of the best way of preparing the part of the plant used, makes an interesting story.

In Arabia and Egypt the beverage was made from coffee, the roasted seeds; in western Africa, from kola, the dried seeds; in the Amazon region of South America, from guarana, a brittle mass made by pounding up the seeds to a paste and drying by heat; in China and Japan, from tea, the fermented leaves; in Paraguay and Uruguay, from maté or Paraguay tea, the dried leaves and shoots of a species of Ilex or holly. The Appalache tea (*Ilex cassine*), which grows from Virginia to the Gulf of Mexico, contains 0.12 per cent. of caffeine and 2.4 per cent. of tannin (Blyth, 1909). Having no caffeine plants, the inhabitants of Mexico and the West Indies made their stimulating beverage of the fermented seeds of the chocolate plant, which contain the close relative, theobromine. Maté contains about 1.3 per cent. of the alkaloid, tea, 1 to 4 per cent., coffee, 0.6 to 2 per cent., kola, 1 to 2 per cent., and guarana, 3 to 6 per cent.

Preparations and Doses.—*Caffeine* (caffeina) is soluble in 46 parts of water and 54 of alcohol. Dose, 1 grain (0.06 gm.).

Citrated caffeine (caffeina citrata) is a mixture of equal parts of caffeine and citric acid. On account of the feebly alkaloidal nature of caffeine, the citric acid is added in excess. It is soluble in 25 parts of water. Dose, 2 grains (0.13 gm.). This is the favorite preparation.

Effervescent citrated caffeine (caffeina citrata effervescens) is a granular salt which contains 4 per cent. of citrated caffeine, *i. e.*, 2 per cent. of caffeine, with citric and tartaric acids and sodium bicarbonate to make it effervesce when added to water. Dose, 50 grains (about two teaspoonfuls).

Compound acetanilid powder (pulvis acetanilidi compositus) contains 10 per cent. of caffeine, 70 per cent. of acetanilid, and 20 per cent. of sodium bicarbonate, but is essentially an acetanilid preparation.

Guarana is official, and is assayed to contain not less than 3.5 per cent. of alkaloid. It contains much tannic acid. It has one official preparation, the fluidextract, dose, 30 minims (2 c.c.).

Caffeine and sodium benzoate and *caffeine and sodium salicylate* are unofficial double salts which are soluble in twice their weight of water, and can be used hypodermatically. Dose, 2 grains

on control days. There was no fatigue reaction to the extra work.

In calculations, there was marked increase in ability, the stimulation beginning in about one hour and lasting several hours. The morning following the experiment showed without exception a clear improvement over the work of the morning preceding the experiment.

In sick people, the condition of wakefulness and keener perception brought about by caffeine is usually highly undesirable; and in habitual insomnia one of the first things to look out for is that the patient shall not take tea or coffee toward evening.

Medulla.—Caffeine strongly stimulates the respiratory center, and moderately the vasoconstrictor and the vagus centers.

Spinal Cord.—Caffeine stimulates the motor cells and promotes the passage of impulses through the spinal cord in the same manner as strychnine, but to a much smaller degree. (See Strychnine for more detailed study of this property.) It, therefore, increases reflex activity, and tends to improve the "tone" of muscle; and in marked amounts may cause twitching of the limb and face muscles. In the laboratory it is often noticed that an animal lightly anesthetized with ether or chloroform will become conscious and recover his reflexes if a hypodermic of caffeine is administered.

Muscle.—If the gastrocnemius of a curarized frog is painted with a weak solution of caffeine, or if caffeine is injected into its supplying artery, the muscle will contract more promptly and to a smaller stimulus, and will lift a heavier load, *i. e.*, its irritability and its strength are increased by the direct action of the drug. The total work of the muscle before fatigue sets in is also increased. Such direct stimulation occurs in both striated and cardiac muscle, but not to any great extent, if at all, in smooth muscle, though the latter may be improved in tone (Sollmann says that smooth muscle is stimulated). From overdoses the typical phenomena of fatigue come on early, the muscle being poisoned. In frogs, large doses induce a stiffening of the muscle like that of rigor mortis; in mammals this effect is not seen, as death takes place before this stage is reached.

Power and Endurance.—Human experiments with the ergograph show greater power and greater endurance of the finger muscles. In comparative experiments with whole companies of soldiers on the march under like conditions, Leistenstorfer, for the German government, found that when the soldiers were well supplied with food, those that were given tea or coffee could endure more prolonged and more severe marches than those that did not get tea or coffee. If no food was supplied, fatigue

Aur.

Ven.

B. P.

Fig. 31.—Caffeine, 5 mg. per kilo, resulted in increased contractility of auricle and ventricle (down-stroke), and a rise in blood-pressure from 68 to 82 mm. The effect was somewhat lasting. Chloroform, 10 breaths, diminished the contractility of both auricle and ventricle, and caused a fall in blood-pressure from 76 to 56 mm. (Tracing made by Dr. C. C. Lieb.)

it would have greater power than this to bring a low blood-pressure to normal is problematic. At the same time this dose of 5 grains sometimes induces undesirable nervous effects, and cannot be repeated at very close intervals without risk of overstimulation of the cerebrum and spinal cord.

Whether or not Sollmann's finding that the systemic arteries are dilated by a peripheral action can apply to small doses in human beings remains to be proved; but in any case caffeine never constricts the arteries that are not under the control of the vasoconstrictor center, viz., those of the lungs, the cerebrum, and the heart. In experimental work the coronary arteries are regularly dilated, and this may be an important factor in the emergency stimulation of the heart. Cushny suggests that it may be secondary to the direct cardiac stimulation. The arteries of the kidneys are also dilated.

Caffeine as a circulatory stimulant is, therefore, purely an emergency drug, and not one to be used repeatedly. It can in no sense do the work of digitalis. We are inclined to think that much of its apparent value in conditions of low blood-pressure is due, not to circulatory stimulation, but to stimulation of the central nervous system, the brain, cord, and respiratory center, the improvement in muscular tone and respiratory and mental vigor being important in conditions of general weakness.

Respiratory System.—Caffeine is a stimulant of the respiratory center, the inspirations being increased in both depth and frequency. In the laboratory this stimulation is best seen after the center has been depressed by narcotic drugs, such as morphine. Toxic doses may induce oppressive breathing from excessive action of the respiratory muscles, and eventually exhaust the center, causing asphyxia and death.

Metabolism is increased by large doses, with a slight rise in temperature. From ordinary amounts of coffee or tea there is no essential effect. Magnus measured the oxygen intake during one-hour periods for three hours after the administration of coffee. After 15 grams of coffee (amount for about two cups) made into a beverage, there was from 3 to 6 per cent. decrease in oxygen intake; after 20 grams there was from 1 to 4 per cent. increase, and after 25 grams, from 6 to 11 per cent. increase, this last being associated with greater motor and reflex activity and stronger pulse.

Excretion is fairly rapid. Caffeine tends to lose its methyl groups as it passes through the body, with the formation of dimethyl and monomethyl xanthines, xanthine, and urea; and these, with perhaps some unchanged caffeine, are excreted in the urine. According to most investigators there is no increase

in a normal kidney, yet without producing diuresis. And in one of his experimental animals caffeine caused abundant diuresis without producing any increase in the volume of the kidney, *i. e.*, without dilatation of the vessels. In uranium nephritis there was a stage in which caffeine, sodium chloride, sodium sulphate, urea, and dextrose all produced vascular dilatation, yet caffeine

a *b*

Fig. 32.—Normal dog. I, Drops of urine. II, Kidney volume. III, General arterial pressure: *a*, Before caffeine; *b*, fourteen minutes after caffeine (from Pearce, Hill, and Eisenbrey).

was the only one that produced diuresis. His inference was that the diuresis resulted from stimulation of the tubule cells, which are not affected by the other substances.

These experiments, with many others of a like nature, seem to indicate that the diuresis of caffeine is not at all through a circulatory action, but is due to a direct action of the caffeine on the cells of the renal tubules. (See also under Diuretics.)

But whether the action is stimulation of the tubule cells or interference with reabsorption, or both, has not been finally determined. Overdoses cause no harm to the kidney, but from continued use, as in coffee- and tea-drinking, the diuretic power becomes less.

In caffeine diuresis there is increased excretion of certain sub-

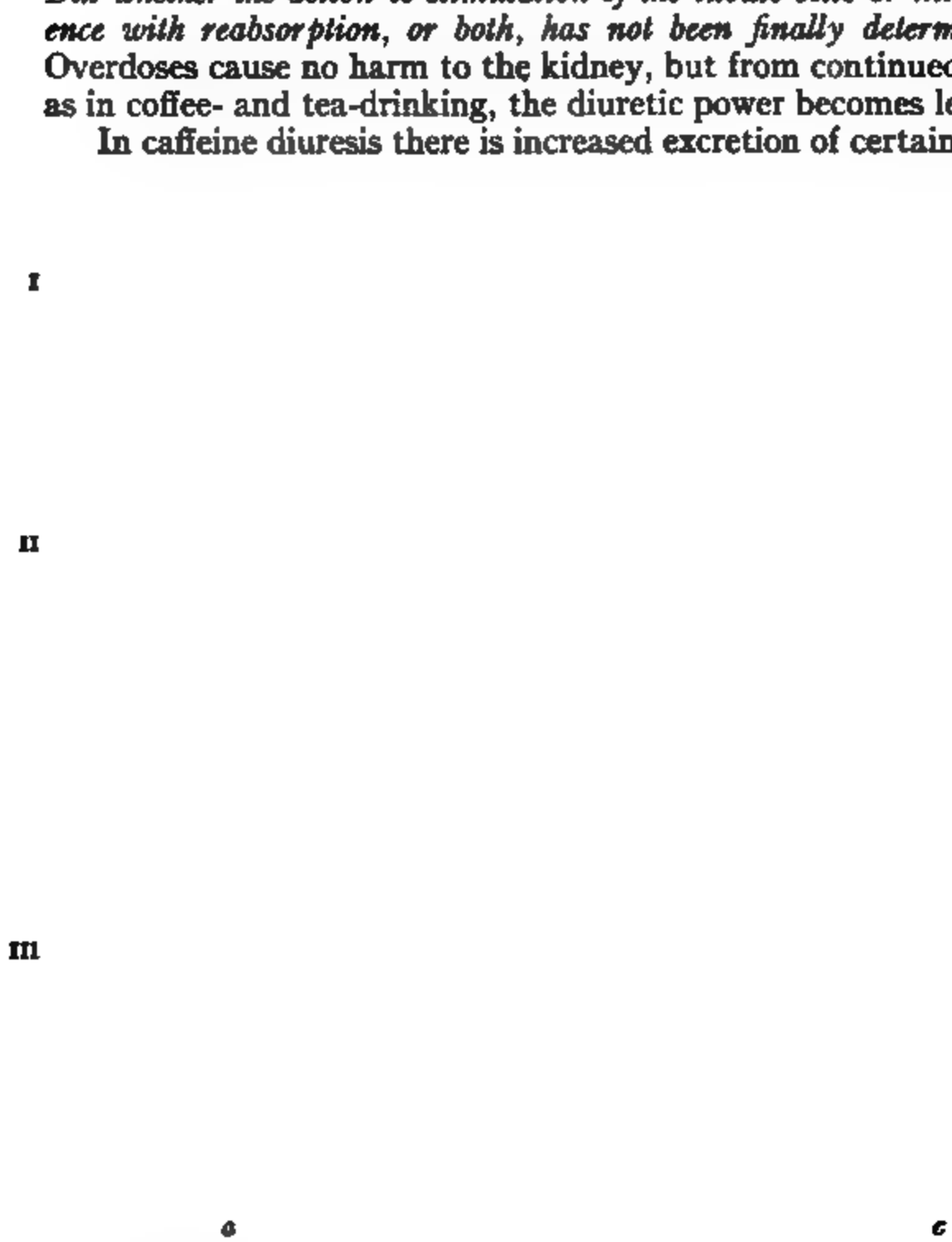


Fig. 33.—Dog after vascular nephritis produced by arsenic: *a*, Before caffeine; *b*, eight minutes after caffeine; *c*, twenty-two minutes after caffeine. I, Drops of urine II, Volume of kidney. III, General arterial pressure (from Pearce, Hill, and Eisenbrey).

stances that are known to be excreted by the tubule cells, as urinary pigment and creatin. Salant and Ringer (1912) find the latter increased 100 per cent. or more in rabbits.

As with other diuretics, the more water there is in the body, the more readily is diuresis produced. V. E. Henderson has shown that when the body is poor in water, caffeine fails as an excitant to secretion, though it brings about the usual dilatation

over, tea and coffee are so much used that caffeine has often lost its influence to a greater or less degree. These three things, then, must be remembered:

1. Caffeine promotes wakefulness and nervousness.
2. It increases the perceptions.
3. Its dose is uncertain, because of marked variations in individual susceptibility.

Administration.—Ordinarily, coffee or tea may be employed, or the citrated caffeine given in one-grain tablet triturates. In collapse, hot strong coffee may be given by mouth or by rectum; or the salicylate or benzoate of sodium with caffeine may be given hypodermatically.

CAFFEINE ALLIES

Theobromine, occurring in chocolate to the extent of 0.3 to 2 per cent., and *theophylline*, which occurs in minute quantities in tea-leaves, but is manufactured synthetically for the market, are isomeric dimethylxanthines.

Theobromine stimulates both cardiac and voluntary muscles to some extent, and has the diuretic power of caffeine. But it is preferred as a diuretic because it lacks the undesirable central effects. For, having no vasoconstrictor action and but little stimulating effect upon the brain, it may be given in much larger doses without the production of wakefulness. The dose is 10 grains (0.6 gm.), given in capsule or powder three or four times a day. As it is insoluble and but slowly absorbed, its soluble combination with sodium salicylate, known as *diuretin*, or that with sodium acetate, known as *agurin*, may be preferred. Their dose is 20 grains (1.3 gm.). They are not official. We have many times noted a very great rise in the urine flow of dropsical patients after theobromine or diuretin.

Theophylline (theocine) has the same action and dose, but it is more irritating to the stomach, so that nausea is not infrequent, and it has some of the central effects of caffeine (Thomas). Theocin-acet-sodium is a soluble salt of this alkaloid.

THEOBROMINE AND CAFFEINE BEVERAGES

The ones that are in more or less universal use among civilized people are coffee, tea, and chocolate. Most of our coffee comes from Brazil, our tea from Japan, China, and India, and our chocolate from the West Indies. The use of caffeine-bearing parts of plants as beverages in various parts of the world has already been spoken of. The dried coffee-seeds are roasted and then ground before use. Roasted coffee contains 0.6 to 2 per cent. of caffeine, a small amount of caffeol (caffeon), and a large

The amount of tea used in making a cup represents 1 or 2 grains (0.06–0.12 gm.) of caffeine, and the coffee per cup 1 ½ to 3 grains (0.1–0.2 gm.), but always some of the caffeine is left behind. Tea-leaves contain more of the caffeine than coffee, but much less tea is used per cup.

Pharmacologic Action.—Besides the caffeine action, coffee derives some of its properties from the empyreumatic oil, caffeol. This is somewhat stimulating to the cerebrum, but in the alimentary tract is a local irritant. Pincussohn has found that coffee results in a prompt increase in the amount and the acidity of the gastric juice; and it is a well-known fact that on the intestines the beverage acts as a laxative, promoting peristalsis. These factors may not be of importance in normal persons, but they become so in hyperesthetic states of the stomach (hyperchlorhydria, hypersecretion, and gastrosuccorrhea) and in diarrhea, so that coffee may be contraindicated.

Tea seems to have a more immediate stimulating effect, either because of its volatile oil or because absorption is more rapid. In "strong" tea the local action in the alimentary tract is due chiefly to its tannic acid. This tends to lessen gastric secretion, to retard absorption, and to induce constipation, so that tea which is strong in tannic acid may decidedly interfere with digestion. But because it contains less extractive matter than coffee, properly made tea, *i. e.*, tea without much tannic acid, is less disturbing to the stomach than coffee. In nervous dyspepsia both tea and coffee are harmful because of the caffeine effect on the nervous system.

Coffee and tea are not nutritive in themselves, and require no digestive process for their absorption. But the addition of milk or cream and sugar changes them into food. In tea the tannic acid precipitates the coagulable protein of the milk, but this precipitate digests in the gastric juice. In some instances the milk and cream have a desirable effect by lessening the local irritant action in the stomach, and by retarding the absorption of the caffeine.

As therapeutic amounts of caffeine are directly antidotal to the cerebral effects of alcohol, the after-dinner demi-tasse may have a special use when wine has been drunk at the dinner. As a hot drink which contains a volatile oil it may also be slightly stimulating to the stomach. However, its reputation as an aid to digestion depends more on habit than upon any intrinsic power in the stomach.

The coffee and tea habits are common among brain-workers (students, writers, etc.) and those who must remain awake at night (nurses, journalists, etc.). The tea habit is especially

mine (according to some authorities, also caffeine up to 0.35 per cent.), 10 per cent. of starch, 15 per cent. of vegetable protein, and 30 to 50 per cent. of a peculiar fat which is known as cocoa-(cacao) butter. (See Fats, Part I.) Pure chocolate is not pleasant to the taste, so for eating and drinking it is regularly sweetened with sugar and often flavored with vanilla. It is highly nutritive, and has been shown by Weissmann, Zuntz, and others to be almost completely digestible, but the fat acts in the stomach to retard both the secretion of gastric juice and the motor functions, *i. e.*, the emptying of the stomach, so chocolate cannot be taken in large quantities. Neumann replaced a fixed allowance of bread, sausage, pork, sugar, and cheese with an amount of cocoa and cocoa-butter of equal caloric value. The diet was moderately satisfactory, but he developed a severe headache which he attributed to the theobromine.

Cocoa is a powdery preparation, made from chocolate by removing a portion of the cocoa-butter by hydraulic pressure, with or without heat. The dried residue is ground to a very fine powder, so that it may be more readily mixed with water. The proportion of theobromine in cocoa is thus somewhat higher than in chocolate, while the fat is less, constituting only 15 to 30 per cent. Inferior cocoas are made by diluting the chocolate with starch, thus reducing the theobromine as well as the fat. The so-called Dutch process is one of partial saponification of the fat with an alkali, to make it miscible with water.

The beverage "cocoa" is made by boiling the cocoa powder with water or milk for at least five minutes, so that its starch may be properly hydrolyzed; otherwise it is nothing but a crude mixture from which the powder tends to separate. When it is made with milk and is sweetened with sugar, it has a high food value; a cupful of such a beverage, prepared with about 10 grams of cocoa, giving a nutritive value of perhaps 250 calories. Such a drink may sometimes be taken by invalids for its food value.

Chocolate is sometimes made into a beverage, but it contains so much fat and requires so much sugar that it is rich and sweet and is heavy in the stomach. It is not suited for invalids.

Cocoa and chocolate have the properties of theobromine, but kidney tolerance is soon established, so that no "diuresis" results from the habitual cup.

NUX VOMICA

Nux vomica is the dried ripe seed of *Strychnos Nux-vomica* (Fam. *Loganiaceæ*), yielding, when assayed, not less than 1.25 per cent. of strychnine. It is native in India, Cochin-China, and Australia.

leg below the ligature, where it can act locally on nerve-endings and nerve-trunk. The reflexes are still intact, because the nerve is left outside of the ligature, but the strychnine does not get to the spinal cord because the circulation is cut off. The prick of a pin below the ligature now meets with just the usual response; therefore the strychnine does not stimulate the nerve-endings or nerves, either sensory or motor. If, now, strychnine is injected above the ligature, the prick of a pin below the ligature results in convulsions.

2. *Poulsson's Experiment.*—Dip a frog in 5 per cent. cocaine solution until its skin is just anesthetized, so as to cut off any afferent impulses from the surface; then give a large dose of strychnine, and no convulsions result. Now generate afferent impulses by stimulating the nerve-trunks, and convulsions follow.

3. *Claude Bernard's Experiment.*—Cut the posterior nerve-roots to prevent afferent impulses from getting to the cord, strychnize the frog, and no convulsions result. Stimulate the central cut end and convulsions follow, whether the roots have been cut peripheral or central to the ganglia.

These experiments show—(1) That the drug does not act upon the peripheral nerves or the posterior root ganglia. (2) That it does not of itself produce motor effects. (3) That it causes increased motor response to afferent impulses, *i. e.*, to external stimuli.

The convulsions are, therefore, reflex in nature, the strychnine acting on structures in the cord itself and resulting in greatly increased reflex excitability.

What is a reflex? If the eye is exposed to a light, the pupil contracts; if some irritating dust gets into the nose, it causes sneezing. These are motor reflexes. If about dinner time the appetizing odor of food is recognized, the stomach begins to secrete gastric juice; if a substance of bitter taste gets into the mouth, the saliva flows. These are secretory reflexes. In each case there is some peripheral stimulus, these actions not occurring otherwise, and the response is involuntary. A reflex, then, is an involuntary secretory or motor response to an afferent impulse.

Reflex actions are usually purposeful and definite, the same kind of response regularly following stimulation at a given place. A piece of dust on the conjunctiva ordinarily results in instant closure of the eye; a teaspoonful of mustard placed in the stomach regularly results in vomiting; the dipping of a frog's hind leg in acetic acid regularly results in a drawing of the leg away from the offending substance and an attempt to wipe it away with the

other leg. The afferent impulses, therefore, do not travel at random to any motor cells, but would seem to travel to those motor cells which can produce the proper purposeful motor response. That is, for each afferent impulse there seems to be in the cord one particular path or group of paths along which it travels to reach the motor or secretory cells, this one path ordinarily being open to it, while all other paths are closed to it. By training, certain new paths are opened up, or, in other words, actions which are at first voluntary become reflex, as in piano-playing, skating, and most of our activities. At first the will is necessary to insure the desired response to the stimulus, as that the finger shall strike a certain key of the piano when the eye sees a certain printed note. But by constant repetition a path is established so that the player comes to strike the proper key involuntarily as soon as the eye perceives the note.

Reflexes are of three kinds, viz.:

(1) The *simple* reflexes, which involve only one muscle, as in winking the eye. (2) The *coördinated* reflexes, in which, during the contraction of one set of muscles, there is inhibition of the opposing muscles; these are the ordinary purposeful reflexes of our bodies. (3) The *convulsive* reflexes, which are incoördinated because all the muscles are stimulated, and there is no inhibition. Since all the muscles contract, the stronger predominate. Convulsive reflexes are exaggerated, purposeless, and harmful, and are due to some derangement of coördination.

How does strychnine produce convulsive reflexes? Baglioni (1900) performed an experiment which has become classic. He exposed the spinal cord of a decapitated frog at the brachial plexus, and removed the pia with its vessels to cut off circulatory connection with the parts of the cord above and below. He then painted the denuded area with a solution of strychnine, and thus poisoned the part of the cord through which afferent impulses from the fore-limb would have to pass, but did not poison the rest of the cord.

1. On stimulating the hind-limb, he got the usual normal reflex response, the poisoned area being beyond the influence of such a stimulus. When he pinched the foot, the leg was drawn up; if he placed a drop of acetic acid upon the leg, the other leg would be drawn up to wipe it off. This proved that the sensory nerves, the synapses, and the motor cells in the lower part of the cord were unpoisoned and acting normally.

2. But when he pinched or pricked one of the fore-limbs or dipped it in acid, there resulted a convulsion of the whole body, both hind-limbs and fore-limbs being involved. In other words,

Hence the action of strychnine upon the spinal cord may be thought of as not only to facilitate the passage of afferent impulses to their usual motor cells, but to open up the paths to the other motor cells, so that the impulses may reach and affect cells ordinarily beyond their influence. In other words, strychnine *increases reflex activity by facilitating the passage of afferent impulses* in the cord (across and up and down the cord). It may directly stimulate the motor cells themselves, but this is not proved.

Sherrington's Theory.—As has been pointed out, a certain stimulus leads, normally, through coördination, not only to contraction of a certain group of muscles, but also to relaxation of the opposing group; and the same stimulus, after a toxic dose of strychnine, induces contraction not only in the usual group, but also in the antagonists. Therefore, under strong strychnine stimulation all the muscles contract, so that, of two sets of opposing muscles, the stronger regularly predominate. For example, if an animal poisoned with strychnine attempts to open its mouth, both the opening and closing muscles are excited, and as the closing muscles are the stronger, the mouth becomes all the more tightly closed. If a man under an excessive dose of strychnine tries to walk, his gait is spastic, and his legs are more or less stiff, because all the muscles are in an excitable contractile state. Sherrington's belief is that the strychnine overaction is due to a change of the usual relaxation or inhibition of the opposing muscles into contraction or excitation, and the will is in complete abeyance. This well explains the exaggerated and convulsive reflexes, and the spasticity, but not the wide-spread response to a stimulus.

Following up this theory, Bayliss has been able to show that, after poisonous amounts of strychnine, stimulation of the depressor nerve will result in a rise in arterial pressure, *i. e.*, the depressor nerve is no longer an inhibitory nerve, but an excitatory nerve.

Tone.—Tone is a condition of readiness to respond to stimulus. All the muscles, both voluntary and involuntary, are in a constant state of tone, *i. e.*, they are in a condition of slight contraction, so that they are drawn up in readiness to work the moment a stimulus comes. One or two experiments to determine the nature of muscular tone are of interest:

1. If a frog is decapitated and the sciatic nerve of one side cut, the leg on the cut side is more relaxed than the other leg, *i. e.*, severance of the leg from its connection with the central nervous system results in greater relaxation than normal, or loss

of its tone. It is evide
the reception of stimuli

2. If a frog's skin
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effect on blood-pressure is very slight, if any. In cases of general weakness the improvement in general muscular tone may have a good effect upon the circulation, but it is a mistaken idea among physicians that strychnine is a direct stimulant to the heart.

To test strychnine clinically, Cook and Briggs injected $\frac{1}{60}$ to $\frac{1}{10}$ grain (0.001–0.006 gm.). In persons ill enough to be in bed, they obtained a slow rise of pressure lasting from one to four hours. There was no effect on the pressure in normal persons or in patients that were moribund. Richard C. Cabot (1904) made about 5000 observations of the arterial pressure before and after strychnine in 50 fever cases, including 31 of typhoid and 4 of pneumonia. In 32 of the 50 cases the drug was given by mouth, in 18 hypodermatically. The usual daily dosage totaled $\frac{1}{8}$ grain (0.08 gm.). In 16 cases there was a rise in blood-pressure of 5 mm. or more; in 24 cases no change in blood-pressure, and in 17 cases a fall of pressure; the average change in blood-pressure was no greater than in that of the controls (18 cases). These experiments must not be too convincing, however, for we have evidence in man that the circulation may be greatly improved without the arterial pressure being raised. (See Digitalis.) Yet they are in line with the findings of the experimental laboratory.

During a convulsion the blood-pressure is very high, because of the great general muscular contraction, but this is of no interest to us in therapeutics. The skin vessels, especially those of the face, may be dilated from a special vasodilator action.

Respiratory.—Large therapeutic doses cause a deepening and quickening of respiration from stimulation of the respiratory center. Large poisonous doses overwhelm and quickly exhaust the center. Death takes place from asphyxia, due either to the setting of the respiratory muscles during a convulsion, or to exhaustion of the respiratory center (between the convulsions).

Under therapeutic doses, the *bronchial muscles* are improved in tone, so the drug may be useful in relaxed conditions of the bronchi; while in spasmodic conditions, as in bronchial asthma, it will be harmful.

In *cough* the reflex excitability is increased, so that when there is abundant secretion to be coughed up, strychnine may change a weak, ineffective cough into an effective one. But when the cough is from a dry or tickling throat and cannot be made effective in getting rid of the offending stimulus, strychnine only uselessly increases the cough and distresses the patient.

Metabolism.—Because of the heightened muscular tone there is some increased metabolism, as shown by increased absorption

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General Anesthetics

The ones in common use are: Ether, chloroform, nitrous oxide, and ethyl chloride.

As ether and chloroform have uses in therapeutics which do not involve the production of general anesthesia, we shall first take up their general pharmacology and therapeutics, and afterward their special uses as anesthetics.

ÆTHER

Ether, or ethyl oxide, $(C_2H_5)_2O$, is obtained by distilling a mixture of sulphuric acid and alcohol. It is a very volatile, light, colorless, limpid liquid, with a burning, unpleasant taste and a characteristic penetrating odor. It boils at about 35.5° C. (96° F.), and should, therefore, boil when a test-tube of it containing some broken glass is held for a time closely grasped in the hand. It is highly inflammable, and its vapor mixed with air is explosive. It mixes freely with alcohol and chloroform, and is a solvent of resins, fats, oils, adhesive plaster, and collodion. In water it is soluble up to about 10 per cent. (U. S. P.) (Moore and Roaf say 8 per cent. in water and 11 per cent. in blood-serum). Its chief impurities are acids, acetaldehyd, and peroxides. Even in originally pure specimens these impurities may develop in the presence of light and air. They are removed if the vapor is passed through water.

Preparations and Doses.—

Ether (æther), by mouth, 15 minims (1 c.c.).

Spirit, 32.5 per cent., 1 dram (4 c.c.).

Compound spirit—Hoffmann's anodyne (ether, 32.5 per cent.; and ethereal oil, 2.5 per cent.), 1 dram (4 c.c.). This has a sharp, unpleasant taste, but is the favorite preparation for stomach administration.

Pharmacologic Action.—Ether is a general protoplasmic poison.

Skin.—If applied to the skin and allowed to evaporate, ether blanches and cools the part by its rapid evaporation; if it is applied in the form of a fine spray, it evaporates so rapidly that the part is numbed by the cold or may even be frozen. If applied to the skin and not allowed to evaporate, it irritates and is rubefacient.

Mucous Membranes.—To these it is very irritant, so for administration by stomach it requires dilution with water, and for administration by the lungs it requires dilution with air or oxygen.

Alimentary Tract.—It has a burning, unpleasant taste, irritates the mouth, and induces a reflex flow of saliva and mucus.

Pharmacologic Action.—Chloroform is a general protoplasmic poison of considerable destructive power. If concentrated, it will cause the death of tissues with which it comes in contact; and even when dilute, as in the blood, it can readily produce degenerative changes in various organs of the body. This striking property seems to be common to various hydrocarbons which contain chlorine.

Microörganisms.—Chloroform is antiseptic, and even in such a dilute solution as "chloroform water" (½ per cent. in strength) will retard putrefaction and fermentation, as in urine.

Local.—It is less volatile than ether, so is less cooling to the skin, and its tendency is rather to irritate than to soothe. If it is dropped on the face from a chloroform inhaler and prevented from ready evaporation, it will make a decided burn. In liniments, if evaporation is prevented by covering with flannel or oiled silk, it is counterirritant.

Alimentary Tract.—Undiluted, it is very irritating to throat and stomach; but its official preparations, being very dilute, are sweet to the taste and pleasant carminatives. They are also soothing to the stomach and antemetic. It is said that the activity of rennet and pepsin is promoted by solutions of less than 0.5 per cent. strength, and retarded by strong solutions.

Heart.—In perfusing an isolated heart, the addition of a small amount of chloroform results in a momentary strengthening, followed very quickly by muscular weakness, the heart soon becoming dilated and the beats small and ineffective. The drug is a strong poison to cardiac muscle. Sherrington and Sowton found that in a perfusion fluid a strength of 0.05 per cent. of chloroform was sufficient regularly to arrest the heart, but that restoration would take place on returning to pure saline. That is, when the osmotic pressure of chloroform in the cardiac cells is below a certain limit, the heart beats again. If too strong chloroform is used, the heart cannot dissociate itself from the chloroform and death ensues.

Levy and Lewis (1912), experimenting with cats, found that light anesthesia, *i. e.*, with the tension of chloroform vapor in the inspired air between 0.5 and 1.5 per cent., regularly produced irregularities in the action of the ventricle, of the types described under "Digitalis" as due to excessive irritability. They observed paroxysmal tachycardia (of ventricular origin), premature ventricular contractions, and ventricular fibrillation. The increase of the vapor tension to 2 per cent. was regularly followed by the disappearance of the irregularity.

With the low-tension vapor, a small intravenous of epinephrine chloride produced the worst form of irritability, viz.,

a *b*

Aur

Ven.

B. P.

Fig. 36.—Chloroform, 10 breaths, (*b*) diminished the contractility of both auricle and ventricle, and caused a fall in blood-pressure from 76 to 56 mm. Caffeine, 5 mg. per kilo, (*a*) resulted in increased contractility of auricle and ventricle (down-stroke), and a rise in blood-pressure from 68 to 82 mm. The effect was somewhat lasting. (Tracing made by Dr. C. C. Lieb.)

ventricular fibrillation, which usually means immediate death; with the higher tension vapor a small intravenous of epinephrine produced the irregularities which had been observed to result from the low percentages of chloroform alone.

Of considerable importance in anesthesia is the finding of Cushny and Edmunds that the heart may be dilated and very weak before there is any noteworthy change in its rate.

Arteries.—On passing chloroformized blood to the cerebral circulation without letting it get into the general circulation (*i. e.*, by a crossed circulation between two animals), there is a momentary rise in arterial pressure, followed quickly by a fall; that is, the vasoconstrictor center, after a primary irritation, is depressed. Bayliss, who has done much work on inhibition, thinks that the vasoconstrictor center is changed by chloroform so that afferent impulses, which normally result in vasoconstriction, now result in vasodilatation. (See Sherrington's theory under Strychnine.)

In some cases the destructive action results in fatty degeneration of the heart, the cardiac ganglia, and even the arteries. This is particularly likely to be the case after the prolonged administration of chloroform for anesthesia, or the repetition of its administration as an anesthetic within a day or two. In anesthesia, death sometimes takes place from collapse, due to depression of the heart and arterial muscles or to ventricular fibrillation. In the early stages of the anesthesia, before the patient is fully anesthetized, death may be due to powerful reflex stimulation of the vagus and vasoconstrictor centers, the latter causing abnormal peripheral resistance against a weakened heart. Muehlberg and Kramer, by the injection of a few minims of chloroform into the carotid artery or jugular vein of laboratory animals, obtained intense stimulation of the vagus and vasoconstrictor centers with heart failure.

Respiratory.—There is a decided depression of the respiratory center, preceded by a very short period of stimulation. In some cases respiratory paralysis is the cause of death, and in experiments with the much diluted vapor the respiration regularly ceases before the heart; but the heart is too weak to permit resuscitation. In the throat and bronchi, if the vapor is properly diluted, it is not irritating and may even be soothing, so that cough or bronchial irritation may be less after the anesthesia than before (Bennett).

Nervous System.—The effects are practically those of ether, the cerebral and spinal depression, however, following more rapidly and from a much smaller amount of drug. The highest intellectual functions are depressed first, then, in succession,

tyrosin. These effects are evidences of increased destructive metabolism with incomplete oxidation.

Therapeutics of Chloroform, Aside From its Use as Anesthetic.—*Externally.*—(1) In liniments, as a *rubefacient* for muscular, joint, and neuralgic pains. (2) On cotton in a decayed tooth for *toothache.*

Internally.—(1) As a mild and pleasant *carminative* in flatulence or colic—the water or spirit. (2) As an *antemetic* in refractory cases of vomiting—one dram of the water every hour. (3) As *antihysteric* and cerebral sedative—the spirit.

The **Chloroform habit** is not uncommon, the sweet taste and narcotic action making the drug a rather pleasant dose. The effects of the habit are similar to those of the chloral habit. (See Chloral Hydrate.)

Narcosis Theories.—There are several theories as to the manner in which narcotic drugs reach the cerebral cell contents, and as to how they act to produce anesthesia. The best known are:

1. *The Meyer-Overton*, which was propounded by Meyer and Overton independently. It is that these drugs exert their main action on the central nervous system, because they are taken up by the fats and lipoids which abound there, and so are held in considerable amount in contact with the cell-structures. The lipoids are lecithin, cholesterin, cerebrin, protagon, etc. According to these authors, the anesthetic property increases with the solubility in fats and lipoids and the insolubility in water. The relation of the activity of hypnotics and anesthetics to their solubility in lipoids is certainly a striking one, and there is a very large amount of evidence supporting this theory, which is the one most generally accepted. It, of course, merely indicates how the anesthetic gets to the nerve-cell, and not what takes place in the cell.

2. *The Theory of Moore and Roaf.*—They believe that narcosis or anesthesia is due to a change in the protoplasm of the cerebral cells by the formation of loose compounds of ether, chloroform, etc., with the cell proteins, and that this results in limitation of the activities of the cerebral protoplasm. On account of the instability of the compounds, these remain formed only so long as the vapor-pressure of the anesthetic in the blood is maintained; so on stopping the administration of the anesthetic the narcosis soon ceases. In the words of Moore and Roaf, that "a certain amount of the anesthetic will be taken up by the lipoid in a physical fashion there can be no doubt, because of the high solubility of these anesthetics in such lipoid substances. But we hold that the portion of the anesthetic so taken up and

held by the lipoid is passive and not active, and that it is the portion taken up by the protein which is active in paralyzing protoplasmic activity and producing anesthesia. It is a matter of common knowledge that the greater the amount of fatty tissue in a subject undergoing anesthetization, the greater is the amount of anesthetic required. The portion of anesthetic absorbed by the lipoid is imprisoned, and more anesthetic must be given in order to raise the (vapor) pressure of the anesthetic sufficiently to cause combination between cell-protoplasm and anesthetic, with resulting anesthetization."

The one theory assumes that the ether dissolved in the fats and lipoids is the anesthetic ether; the other considers this ether lost or imprisoned, and the anesthetic ether to be only that which enters into combination with the cell proteins.

3. *That of Verworn.*—He accepts the Meyer-Overton theory as showing the properties necessary for an anesthetic to reach the field of action. But he goes on to give an explanation of the cause of the depression of the activity of the cerebral cells. He shows that in narcosis there is interference with the oxidative processes of the cells, or, in his own words, "the factor which produces the characteristic symptom-complex of narcosis is under all circumstances the suppression of the power to carry on oxidations." His theory is that narcotics render the oxidases (the oxygen carriers) in living tissues incapable of carrying oxygen. He shows that this may take place in any cells of the body, but that the cells of the cerebral cortex are especially sensitive to lack of oxygen, and are depressed with very much less of the narcotic than is necessary to depress the nerves and muscles.

One of his experiments may be cited: The sciatic nerve of a frog was deprived of oxygen until its irritability was much reduced and its conductivity lost. It was then narcotized with ether. During the ether, oxygen was supplied for a long time, but it had no effect whatever upon the narcosis. Then nitrogen was substituted for the oxygen, and the narcotic was stopped. Still, though the ether passed off, the functions were not restored in the nitrogen atmosphere. After a while the nitrogen was replaced by air, and in one minute the nerve had recovered its conductivity and its irritability. That is, so long as the cell was under the narcotic influence, oxygen had no power to set the cell functionating, but did set it functionating when the narcotic had been removed. Also the mere removal of the narcotic was not enough, but oxygen was necessary to restore the lost functions of the cell.

ETHER AND CHLOROFORM AS GENERAL ANESTHETICS

When one of these drugs is administered in sufficient amount to put the patient into a state of coma, with muscular relaxation and the abolition of nearly all reflexes, the patient is in a condition of "complete general anesthesia." The study of general anesthesia is, then, a study in toxicology; and the production of ether or chloroform anesthesia is the production of acute ether or chloroform poisoning, the patient being drugged into a state of narcosis bordering on collapse.

The objects of general anesthesia are: to abolish pain, consciousness, and muscular resistance. To be useful as a general anesthetic, a drug must be very rapidly absorbable, must act quickly to produce narcosis, and must be very rapidly eliminated; and it must be capable of producing muscular relaxation as well as complete unconsciousness, *i. e.*, abolishing cerebral and spinal activity, without dangerous depression of the vital medullary centers or any permanent effect upon the central nervous system.

As these drugs are highly volatile and their vapor is rapidly absorbed by the lungs, their administration by inhalation is preferred as being more controllable and more easily continued for a long time; but a sufficient dose by mouth or rectum or vein will also produce anesthesia.

We shall take up ether anesthesia first, then compare chloroform anesthesia with it.

For general anesthesia, ether is regularly administered by inhalation, the vapor being diluted with air or oxygen and absorbed by the lungs. To avoid dangerous irritation of the respiratory passages and to prevent asphyxia, the ether vapor must not constitute more than a small percentage of the total ether-air mixture; *i. e.*, it must be diluted with air for administration by the lungs, just as Hoffmann's anodyne must be diluted with water for administration by the stomach. To get the patient quickly into a condition of anesthesia it is necessary that the air-ether mixture shall contain from 4 to 6 per cent. of ether; while to maintain the anesthesia it must be kept of about 3 to 3.5 per cent. strength. It is unsafe to use ether in a strength above 4 per cent. for any great length of time. With a proper adjustment of the amount of air and the amount of ether a patient may generally be kept anesthetized for a long period, even for three or four hours, without any serious symptoms manifesting themselves.

For convenience of study the production of ether anesthesia may be divided into four stages:

1. Local action and blunted perceptions.

cyanotic. If the stomach contains food, there may be vomiting. The pupils are dilated and react to light, and there may be rolling of the eyeballs or strabismus, with the eyelids wide open. The heart continues somewhat rapid and there may be raised blood-pressure. If the patient is an alcoholic, very fat, or robust and athletic, this stage is rather prolonged; and a very large amount of ether, or a vapor concentrated even up to 10 per cent., or the addition of chloroform, may be required to complete the anesthesia.

The **third stage** is that of stupor, *i. e.*, unconsciousness from which one can be aroused only with difficulty. The pupils are contracted as in sleep, the heart is strong and regular and slower than before (though not slower than normal), the breathing is deep and regular, the color of the skin is good.

The intoxication stage is over, but there is not complete anesthesia, for if the knife is used in this stage, the patient will wince, or may be aroused by the pain and try to get up. The muscular relaxation is also incomplete. The pupil dilates with pain and contracts readily to light. The patient may be kept in this stage for any length of time, or may quickly be brought into—

The **fourth stage,** which is characterized by great muscular relaxation and complete unconsciousness, from which the patient cannot be aroused, *i. e.*, coma.

Most of the voluntary muscles are relaxed. An arm or a leg raised in the air falls limp, and the face is expressionless from relaxation of the face muscles. The sphincter ani is one of the last of the voluntary muscles to be paralyzed. The respiratory muscles, of course, are not paralyzed. Smooth muscle loses its tone less readily than voluntary muscle, and intestinal peristalsis is sometimes observed on opening the abdomen. The skin is usually flushed and hot, and is covered with sweat (hence the need of protecting the patient from catching cold). In the mouth and throat saliva and mucus are abundant. The pupils are in mid-dilatation and react so sluggishly to light that their contraction may be difficult to detect. The eye reflexes disappear, the absence of the corneal or conjunctival reflex being one of the indications that the patient is well anesthetized. The heart is regular and of fair force. Its rate is moderately increased. Arterial pressure is good, but in prolonged anesthesia slowly falls. The respiration is regular and may be stertorous or snoring, or may be impeded by the tongue or the collection of saliva and mucus, large amounts of which are secreted in the throat and bronchi (the throat must be kept clean, the jaw and tongue kept forward). The temperature falls, so that the patient

condition of acidosis. If it persists after a few hours, the stomach may be lavaged with a solution of sodium bicarbonate; or 30-grain (2 gm.) doses of sodium bicarbonate may be administered, or 1 ounce (30 gm.) of glucose (Beddard) or olive oil (Graham). *Thirst* is marked, but because of the vomiting tendency cannot be allayed. Most surgeons allow very little liquid for the first few hours, *e. g.*, one or two teaspoonfuls of water each hour or half hour. The thirst is less if the patient drinks freely of water two or three hours before the operation.

(*b*) *Distention of stomach and intestines* with gas, sometimes lessened by carminatives, stupes, enemata, colon irrigations, the continuous rectal drop method of Murphy, or by physostigmine hypodermatically.

(*c*) *Pain in the back*, between the shoulders, or in the small of the back. Lessened by change of posture, special pillows, etc.

2. Untoward Sequelæ.—(*a*) *Of the respiratory organs*—bronchitis, pneumonia, edema of the lungs, or the lighting up of a quiescent tuberculous process in the lung. The danger of pneumonia is said by Müller to be greatly increased if ether is administered a second time within a few days. N. G. Davis and also Stursberg have brought forward some evidence that in some cases the post-ether respiratory troubles may be due to the patients catching cold rather than to ether irritation. Stursberg, in experimenting with dogs, found that if the ether were allowed to evaporate freely there was a surface chilling, with pronounced rise in arterial pressure from reflex contraction of the internal arteries. This did not occur from chloroform. With the open cone, too, the ether refrigeration by evaporation at the mouthpiece makes the inhaled vapor very cold, and this in itself might be enough to irritate the bronchi and lungs. Hence the resort to warmed vapor on the part of some anesthetists, the container being placed in warm water. There is evidence, both pro and con, as to the value of warming the vapor. Seelig (1911) found that the gas inhaled caused no cooling in the trachea, but that the evaporating vapor cooled the air about the patient.

(*b*) *Of the kidneys*—albuminuria and sometimes acute nephritis.

(*c*) *Post-operative Gastric or Intestinal Paralysis.*—Treated by strychnine and lavage, intestinal irrigations, enemata, or eserine, $\frac{1}{40}$ grain (0.0015 gm.).

(*d*) *Local injuries*, as *conjunctivitis*, from ether getting into the eye, or from injury done by the finger of the anesthetist in testing the corneal reflex; and a *sore tongue* from the use of tongue forceps, or from the passing of a suture through the tongue to hold it forward.

has been shown to prevent fatty degeneration of the liver and to lessen post-operative nausea. It has been shown that the dangers of ether are greater in starvation and fatigue, so it is considered wise not to leave the patient without food and rest for too long a period before the operation.

9. *Administering sodium bicarbonate*, ½ ounce (15 gm.) in solution by rectum half an hour before the anesthetic.

INDICATIONS FOR ETHER AS ANESTHETIC

Ether, especially with proper preventive precautions, is preferred to chloroform in almost all cases, including those with heart or kidney disease. It is not employed in cases with severe bronchial or pulmonary inflammation, or in very old age, where the ether intoxication might result in rupture of a sclerosed vessel or in some other injury. In brain surgery Horsley prefers chloroform because of the danger of a rise in general arterial pressure from ether and the resultant extensive oozing of blood; while Crile uses ether because of the special danger, in such surgery, of depression of the medullary centers.

When ether fails to bring about muscular relaxation, as in some alcoholics or very robust athletic persons; or when the secretions of the throat are so abundant as to become dangerous, chloroform alone, or chloroform followed by ether, may be employed. It is reported that in hot countries and at high altitudes anesthesia with ether is difficult to obtain; but Squire (Lancet, 1913) reports the satisfactory use of ether, even with the temperature 120° F. in the shade.

Where a very quick and very transitory effect is desired, as in obstetrics, chloroform is usually preferred. But a number of cases of fetal death from chloroform are reported; and in some cases, though the child is born alive, it never breathes because of the depression of the respiratory center.

CHLOROFORM ANESTHESIA

In the production of anesthesia by chloroform there are four stages, as in ether anesthesia, and the symptoms are the same in nature. But chloroform, properly diluted with air, is not unpleasant to the patient, is scarcely irritating to nose and throat, and is more prompt in producing anesthesia, hence the first and second stages are comparatively short and not so disagreeable, and the stage of intoxication is seldom troublesome. With chloroform a patient may be anesthetized in from two to five minutes; with ether it may take ten or fifteen minutes. The recovery is correspondingly rapid. Again, the amount of ether required is much greater, it being reckoned in ounces, while that

Ordinarily, it is impossible to kill an animal by excessive vagus stimulation, for after a brief period the heart will go on beating again in spite of the vagus. But in the administration of a gas by the lungs the area of absorption is large; and the pulmonary blood, charged heavily with vapor, passes instantly to the left heart and poisons its muscles.

Cases are not reported of excessive vagus inhibition from the use of ether as an anesthetic, but Muehlberg and Kramer have shown that an injection into the carotid artery of as little as 2 minims of ether or chloroform can cause almost instant death in a rabbit. They also show that even if vagus inhibition is prevented the heart is weakened. The conclusion is that when death takes place during the early stages of chloroform administration there are probably three conditions present, viz.: (1) Weakening of the heart due to direct action of the poison. This, absorbed by the extensive lung surface, makes a concentrated solution in the pulmonary blood which passes at once into the left heart and to the coronaries; (2) reflex vagus stimulation and (3) reflex vasoconstrictor stimulation. The combination of these three effects, viz., inhibition, muscle poisoning, and increased peripheral resistance, results in heart failure.

If the chloroform is given to a dog in sufficient dilution with air to avoid the local irritation of the throat, both the vagus center and the throat soon become less sensitive, and then it is impossible to produce this vagus inhibition with any strength of chloroform. Hence the excessive reflex activity of the vagus may be prevented by avoiding too great concentration of the vapor at the outset, or by a preliminary injection of a large dose of atropine, or by thorough cocainization of the pharynx and larynx. (See experiments of Levy and Lewis under Pharmacologic Action above.)

The Second Danger.—We have already learned that chloroform is much more depressing to the muscles of the heart and arteries and to the medullary centers than is ether. This depressing effect is seen almost from the start, while with ether such a depression is not noted except in prolonged anesthesia or from overwhelming doses of concentrated vapor. In addition the chloroform has a special affinity for the heart muscle, so that it is less readily discharged from it than ether. Hence resuscitation is difficult.

These factors make the margin of safety for chloroform a narrow one, the stage of complete anesthesia being much nearer the stage of collapse than with ether. Furthermore, when collapse comes on from ether, the patient may often be restored

rarely been recovered from. A. Weir reports one case of recovery following the administration of 15 gm. of glucose in 500 c.c. of water by stomach (tube through nares) every four hours, and 10 gm. of glucose in 100 c.c. of water by rectum.

The conditions which favor the development of delayed chloroform poisoning are believed to be: Liver abscess, kidney disease, anemia, especially that due to hemorrhage, alcoholism, obesity, the lymphatic diathesis, childhood, previous chloroform anesthesia within two or three days, and prolonged anesthesia.

Several observers have reported acute liver atrophy following chloroform.

To repeat, then, the three dangers in chloroform anesthesia, which are slight or absent in ether anesthesia, are the following:

1. *Sudden death* before complete anesthesia is induced.

2. *Small Margin of Safety.*—The depression of heart and arteries and of the vasoconstrictor and respiratory center, makes a *small margin of safety* between the stages of anesthesia and collapse, and difficulty in restoring the patient after signs of danger are manifest. This is especially true in persons with the lymphatic diathesis.

3. *Delayed chloroform poisoning.*

It is on account of these that the use of chloroform has been quite generally abandoned as a general anesthetic, except in a few special types of cases.

Possible preventive measures are:

1. To prevent vagus stoppage of heart—atropine, $\frac{1}{60}$ grain (0.001 gm.) by hypodermatic, cocaine to throat, or well-diluted chloroform at the start.

2. To retard cardiac and central depression—oxygen, avoidance of too long a period of starvation before the operation, and the use of a minimum quantity of the anesthetic.

3. To lessen or check the fatty degenerations—oxygen and glycogen-forming food (glucose, sugar, etc.), with avoidance of too long a period of starvation before the anesthesia. Hunter recommends that the patient be given a nutritious and easily digestible meal, well sweetened, two or three hours before the anesthetic.

Contraindications to Chloroform.—Diabetes, sepsis, hemorrhage, eclampsia, conditions of much enfeeblement, fatty degeneration, and the lymphatic diathesis.

Acidosis in General Anesthesia.—The development of acidosis following anesthesia, as shown by the appearance of acetone, diacetic acid, and beta-oxybutyric acid in the urine, is a matter of considerable importance.

According to Ewing, Becker found acetonuria in two-thirds

The inhalation methods are:

1. *The Open Cone Method.*—Usually an extemporized cone made of a towel and some paper, with a handful of absorbent cotton or gauze inside to receive the ether. It may be made with a special frame, as the Allis Inhaler. The open cone allows much air to be drawn in, so to get the concentration of ether required to produce anesthesia it is necessary to place a large quantity of ether in the cone and to exclude the air as much as possible by wet towels. In fact, to hasten the process the anesthetist is sometimes tempted to exclude too much air, with resulting cyanosis.

At the commencement, the cone, containing ½ to 1 ounce of ether, is held several inches from the face, but as the patient becomes accustomed to the vapor is gradually brought nearer. In two or three minutes, when the local anesthesia has come on, it is placed down over nose and mouth, fitting closely to the face. If the patient stops breathing, owing to the irritation of the ether, the mask may be removed for a moment, then replaced as soon as he takes a breath of air. Sometimes a change from shallow to deep breathing will send the patient under very quickly, as a large amount of ether is at once drawn into the lungs.

2. *The Drop Method.*—Ether is rapidly dropped, about 150 drops to the minute, upon a large Esmarch chloroform mask covered with flannelette. This is placed close over nose and mouth, and may be wrapped around with a wet towel, so that it fits closely to the face. This method allows free air-supply and reduces the danger of cyanosis to the minimum. Ladd and Osgood, and also Williams and Young, claim that by this method acetonuria is less frequent than with the cone.

3. *The closed inhalers*, Bennett's, Clover's, Hewitt's, etc., are employed with the double purpose of preventing waste of ether and of regulating the relative supply of ether and air. With these a bagful (one or more gallons) of nitrous oxide gas is generally administered first, to shorten the first and second stages, then the ether connection is attached, and the supply of ether and air regulated by valves. There is little waste of ether.

Chloroform is administered by inhalation or intravenously. For inhalation it may be administered by the drop method on an open mask or by a closed inhaler.

1. *In the drop method*, from 60 to 600 drops (4 drops = 1 minim) are required to produce anesthesia, and about 20 to 40 drops per minute to maintain it. A small wire frame covered with flannelette or several thicknesses of fine gauze is used as the mask. At the start the mask is held a few inches from the face, and is gradually brought nearer until it is close to the nose and

keep up a sufficient degree of positive intrathoracic pressure to prevent collapse of the lungs in intrathoracic surgery. This method has now become extensively employed for anesthesia with ether and for nitrous-oxide-oxygen anesthesia.

After a preliminary anesthesia to depress the laryngeal reflex a silk-woven catheter, about No. 22 French, is inserted through the glottis until the teeth are at a mark 26 cm. from its end. Then, with a bellows or pump, operated by foot or power, the air is passed through or over ether in a bottle into the trachea. The gases from the lungs make their escape around the catheter, and this should be small enough to leave ample room in the glottis. The apparatus should bear a manometer for recording the pressure, and the positive pressure should not, in ordinary operations, exceed 10 mm. of mercury, and in intrathoracic surgery 20 mm. At the end of the operation the ether is shut off, and air insufflated for several minutes. From three to six times a minute the air-stream should be stopped to permit collapse of the lungs and the expulsion of some CO_2, which tends to collect in the alveoli. The ether-air vapor should be of about 6 or 7 per cent. strength.

The patient makes light respiratory movements, but the oxygenation of the blood goes on, irrespective of respiration. The color of the skin is good, and the pulse is normal. If the patient vomits on the table, or if blood runs down the throat, as in mouth operations, the positive pressure of the escaping gases prevents aspiration of the foreign material into the lungs.

Following the anesthesia there seem to be no bad effects from the tube or the ether vapor, either upon the glottis, the trachea, the bronch, or the lungs, even in the presence of a respiratory disease; and usually there is no nausea or vomiting. There have been a few deaths reported, generally due to rupture of the lungs from too great pressure, or to puncture of the trachea by a tube that is too long. This last produces interstitial emphysema. These dangers can be eliminated by having a short tube, a manometer, and a careful anesthetist, or by a safety valve set at 20 mm. of pressure.

Githens and Meltzer (1911) showed that double the lethal dose of strychnine given under ether anesthesia by intratracheal insufflation did not cause the death of a single animal.

TREATMENT OF UNTOWARD SYMPTOMS IN GENERAL ANESTHESIA

(*A*) *Cyanosis.*—If this is due to excessive secretion or the falling back of the tongue or jaw, or falling of the paralyzed epiglottis, so as to act as a valve over the glottis, or turning of

the head too much to the side, the condition should be promptly remedied. If there is respiratory weakness, the anesthetic should be stopped and a respiratory stimulant, such as caffeine or atropine, injected hypodermatically. In the laboratory a dog lightly anesthetized with ether or chloroform is likely to become conscious and recover his reflexes if a hypodermic of caffeine is administered. If necessary, artificial respiration and the administration of oxygen may be resorted to.

(*B*) A *rapid*, *weak*, or *irregular pulse* suggests the withdrawal of the anesthetic and the use of saline by rectum or intravenously.

(*C*) *For marked collapse*, the following is the treatment:

1. If from ether, lower head, raise feet, and give free access of air. If from chloroform, keep body level or may precipitate heart failure (Bennett).

2. Keep up body warmth, using hot towels and hot blankets.

3. Inject hypodermatically atropine, caffeine, or camphor (not ether or whisky). Camphor *may* be useful in chloroform collapse, where the heart is the organ at chief fault. (See discussion under Camphor.)

4. If an ether case, give hot saline by rectum; or an intravenous infusion of about 400 c.c. of normal saline solution, to which may be added 10 minims of adrenaline chloride solution. Continuous slow saline infusion for half an hour with 15 to 30 minims (1–2 c.c.) of adrenaline chloride solution is of great advantage. In the light of the work of Levy and Lewis, adrenaline would be absolutely contraindicated in chloroform anesthesia at any stage; yet we have surgical reports of excellent results from adrenaline even after chloroform.

5. If necessary, the limbs may be bandaged from fingers and toes up, or Crile's pneumatic suit applied.

6. Artificial respiration and the administration of oxygen and carbon dioxide. Henderson says that carbon dioxide should not be given in concentration above 6 per cent. Meltzer's method of artificial respiration by intratracheal insufflation or by a suitable mouth-cap may be employed.

7. *If the heart stops*, try rhythmic thumping or pressure over the heart, or rhythmic pressure at a rate of 30 per minute in the epigastrium; in an abdominal operation massage heart through the diaphragm. With a long thin needle inject 10 minims of adrenaline solution and 10 minims of the tincture of digitalis into the cavity of the ventricle, and massage vigorously. The author has resuscitated dogs in this manner. This should not be attempted if the heart is beating.

Ether, whisky, and strychnine hypodermatically have repeatedly been shown to increase the collapse, and electricity to

such rapidity that it freezes the tissues. This makes a local anesthesia of a moment's duration, during which a small cut, as of an abscess or infected finger, or a puncture, as in paracentesis of thorax or abdomen, may be made without pain. The freezing of the tissues sometimes results in sloughing. The spray is sometimes also employed in facial neuralgia.

Systemic Action.—To produce general anesthesia ethyl chloride is vaporized into an inhaler. The patient may be brought into a state of anesthesia in from one to two minutes without any local irritation, but with incomplete muscular relaxation. Recovery when the anesthetic is stopped is almost immediate, and because of this it is a difficult task to maintain the anesthesia for any length of time. (Whiteford has kept the patient under ethyl chloride for thirty-five minutes, and Wiessner for fifty minutes, by pouring 2 or 3 c.c. on the mask every two minutes; Montgomery and Bland, for fifty-four minutes.) A few fatalities have been reported, but, according to W. Lauzun-Brown (Hospital, October 27, 1906), these occurred in the early days of its use. Since then more than 7000 operations have been performed under its administration at the Central London Throat and Nose Hospital without any death. Ware has used it in 8000 cases, and recently Sill has reported its employment with an Improved Ware Inhaler, in 500 tonsil and adenoid cases without untoward symptoms. He says that it takes two to five minutes to produce anesthesia sufficient for the removal of adenoids and tonsils, but the recovery is almost immediate, so that the child can cough and expectorate the blood and adenoid tissue. Vomiting after the anesthesia is not uncommon.

On the average, 5 gm. will produce unconsciousness and abolition of pain in one or two minutes, and maintain it for ten minutes, but the reflexes are not depressed to the point of complete muscular relaxation. Because of its concentrated form and ease of transportation, it being a liquid in glass tubes, and because of its cheapness in the dose used, it has been employed in operations of short duration, in dentistry, and as a preliminary to ether anesthesia.

Ethyl bromide resembles ethyl chloride in its action, but is not quite so volatile, and its use has been abandoned.

INTOXICANTS

ALCOHOL

Common alcohol, grain alcohol, ethyl alcohol, $C_2H_5(OH)$, is made by fermenting a sugar solution with yeast in the presence of nitrogenous substances. The sugar may be that of a fruit-

prepared from starch or wood. Along with the other bodies are produced. The alcohol of commerce by distillation, and contains amyl alcohol and [illegible] constitute its "fusel oil." It mixes freely [illegible] and chloroform, and is a solvent for alkaloids, [illegible] volatile oils, and two of the fixed oils, viz., [illegible] oil. It does not dissolve the other fats and [illegible] plaster or collodion.

Pure alcohol is to be had in three strengths.

[illegible] *alcohol*, at least 99 per cent. of ethyl alcohol; [illegible] cent. (U. S. P., 94.9) by volume. This is not [illegible] commerce, but is known to the trade as "deodorized [illegible] spirit." It is ordinary grain alcohol [illegible] removed, and has a specific gravity of 0.816 at [illegible] *alcohol*, 48.9 per cent. by volume, made [illegible] water and alcohol, which shrink on mixing. [illegible] one or other of the alcoholic drinks is regu- [illegible] than pure alcohol; and these contain, in [illegible] substances which give them their char- [illegible] taste. A large number of pharmaceutic [illegible] alcohol either as solvent or preservative, [illegible] remedies with a large content of alcohol [illegible] Women habitués frequently drink in [illegible] large quantities of eau de cologne, [illegible] hazel, or some proprietary remedy. *De-* [illegible] tax free, is a mixture of 100 parts of high- [illegible] parts of rectified wood-alcohol, and 0.5

[illegible] in common use are of five classes:

[illegible]
[illegible] white wines.
[illegible] wines.
[illegible] liquors, or spirits.

[illegible] **liquors** are prepared from starchy substances, [illegible] grains are ground and boiled with water to [illegible] hydrolyze the starch and form a starch paste. [illegible] barley malt, which contains the ferment dias- [illegible] changes and goes into solution as dextrin, mal- [illegible] To this solution are added hops, which yield [illegible] and a hypnotic substance; then, after filtration, [illegible] fermented by yeast to the desired degree. Then the [illegible] by heat, the fermentation being always stopped

before all the sugars are destroyed. Cheap beers have quassia, gentian, wormwood, or other bitter substitutes for the hops.

The malt liquors contain from 3 to 7 per cent. of alcohol by volume, together with about the same percentage of extractive matter, composed of dextrin, maltose, and colloidal material, and acids of the fatty series, chiefly acetic. They all contain CO_2 gas, so are effervescent. Strauss states that they average about 0.145 gm. of purin bodies per liter. They are acid in reaction, have the action of bitters upon the appetite, and are nutritive. In the stomach they immediately set free the contained CO_2. The sugar bodies also tend to generate gas, and the colloidal material to interfere with the activity of the digestive ferments. None of the malt liquors are official, but those in common use are: Beer, ale, porter, and stout.

Beers ("lager beer") are prepared by slow, cool fermentation (38° F.)—Blyth says 12°–14° C. (53°–57°), by bottom yeast, *i. e.*, a yeast which sinks. Imported beer is usually stronger than domestic, a little higher proportion of alcohol being desired for preservation purposes.

Ales (in British countries called "beer") are fermented at ordinary temperatures (56°–68° F.) by top yeast, *i. e.*, a yeast that floats. They average somewhat more alcohol than beer.

Porter and stout are ales in which the malt has been highly kilned or roasted, so that some of it is changed to caramel. As a consequence they have a very dark color and a caramel taste, and are rich in dissolved substances. Stout is the richer and stronger of the two.

The *liquid extracts of malt* used in medicine are beers containing a small percentage of alcohol, a large amount of nutritive extractive, chiefly sugars, and unchanged extract of malt.

2. The **wines** are made by yeast fermentation of saccharine fruit-juices. They vary considerably in their composition, but regularly contain from 8.5 to 15 per cent. of alcohol by volume, with glycerin, tartaric acid, acetic and other fatty acids, aldehydes, furfurol, amylic, œnanthylic, and other alcohols, certain esters which are produced on long standing and give to the wine its mellowness and bouquet, and albuminous and other colloidal extractive matters. The red wines contain tannic acid; the sweet wines contain dextrose. Kahlbaum of Berlin has separated 12 different esters from wines in common use, acetic ether being that most frequently encountered. Wines are not so nutritive as the malt liquors, and many, such as claret, Burgundy, Rhine, and Moselle wines, contain little or no sugar. With age the tannin, alcohol, and acids decrease, and the glycerin and esters increase. The largest percentage of esters is 0.3 (Dupré).

(*a*) *Those Obtained from Malt Liquors.*—In common use are whisky and gin. ("Schnaaps," in Europe, is prepared from potatoes, and is a cheap whisky; in this country it is a name employed by foreigners for corn whisky.)

Whisky (spiritus frumenti) is described in the Pharmacopœia as "an alcoholic liquid obtained by the distillation of the mash of fermented grain (corn, rye, wheat, barley), and not less than four years old. It contains 44 to 55 per cent. by volume of ethyl alcohol, and in addition minute quantities of various other alcohols, ethers, etc., carried over in the distillation, and acid esters formed on standing." Cheap whiskies are aged by ozone and electricity in three days, and are darkened with prune-juice to give them the color that is properly derived from storage in oak barrels. The fusel oil of whisky is composed chiefly of amyl alcohol and furfurol.

Scotch and Irish whiskies have a somewhat smoky odor from being distilled over peat fires, or being made from malt that is dried over peat fires. They are said to contain traces of creosote and other empyreumatic oils. Irish whiskies usually contain a rather high percentage of alcohol.

Gin is prepared by distillation of fermented rye mash, and redistillation of the product with juniper berries, or sometimes other aromatics, such as cardamom or coriander. It contains a high percentage of alcohol, 60 to 70 per cent., and some volatile oil of juniper, on account of which it is diuretic and carminative. It is a favorite remedy among women for dysmenorrhea. Gin is sometimes called the "compound spirit of juniper."

(*b*) *Those Distilled from Fermented Saccharine Fruit-juices.*—These are known as brandies. Apple-brandy and pear-brandy are prepared from apples or pear cider. But the brandy of commerce and of the Pharmacopœia is that from grape-wine. It is known also as "Cognac" or "French brandy."

Brandy (spiritus vini gallici) is described by the Pharmacopœia as "an alcoholic liquid obtained by the distillation of the fermented, unmodified juice of fresh grapes, and not less than four years old. It contains 46 to 55 per cent. by volume of ethyl alcohol, besides enanthic and other esters."

Rum is the distillate from fermented molasses, and has a slight taste of brown sugar. It varies greatly in strength, but is frequently much stronger than brandy.

5. The **elixirs** are aromatic, sweetened, hydro-alcoholic liquids. They are artificial mixtures, and contain various flavoring substances, sugar, and a large percentage of alcohol. They include the *pharmaceutic elixirs*, and the *liqueurs*, *cordials*, *crêmes*, etc.

activity of the digestive process. But by alcoholic liquids below 20 per cent. in strength pepsin in solution is not injured, and when the proportion of alcohol present does not exceed 10 per cent., or perhaps even 15 per cent., the effect upon proteins and upon the activity of the digestive ferments in the test-tube is practically negative. Solutions up to 2 per cent. in strength have been shown by Chittenden, Mendel, and Jackson to favor the activity of pepsin digestion.

But with alcohol there is a great difference between the actions in a test-tube and those in the stomach; for in the test-tube the alcoholic strength remains the same throughout the experiment, and the products of digestion are not removed, while in the stomach the products of digestion pass away and the alcohol strength becomes steadily less, owing to dilution with gastric juice and mucus and to absorption of the alcohol. We are safe in saying, therefore, that in the human alimentary tract *the influence of moderate quantities of properly diluted alcohol upon the chemic processes of digestion is a negligible factor.*

With the alcoholic drinks, however,—and it is these and not pure alcohol that are in common use both in therapeutics and as beverages,—the other constituents must be taken into consideration. The volatile constituents of wines have been studied by Krantwig and Vogel (Binz), and found to have a pharmacologic action similar to that of alcohol. Their proportion, however, is very small. Chittenden and Mendel have determined that the distilled liquors, which contain the same or similar volatile substances, exert an effect upon the digestive chemistry practically proportional to the amount of their alcohol. Hence if the distilled liquors are diluted to 10 per cent., they have no harmful effect on the chemistry of digestion.

But Chittenden and Mendel found that the wines and malt liquors tend to retard pepsin digestion, even when their alcohol is much below the harmful percentage, so if taken in considerable quantity they are deleterious to digestion. This is because of their organic acids and colloidal constituents, and not because of their alcohol. Red wines, because of their tannic acid, which tends to precipitate protein, have a retarding influence beyond that of white wines.

2. *Action on the Structures of the Stomach-wall.*—As it cannot evaporate from the stomach, alcohol dilates the vessels and gives a feeling of warmth in the stomach. Below a strength of 10 per cent. it has practically no other effect unless taken in too large quantities to be absorbed rapidly. But in strength above 50 per cent., and, to many stomachs, in much weaker dilution, it is powerfully irritant and capable of causing inflammatory

changes. Its local irritant properties depend on its dilution rather than on the actual amount of alcohol involved.

3. *Action on the Functions of the Stomach.*—The chief functions are absorption, motility, and secretion.

(*a*) *Absorption.*—Ordinary amounts of alcohol in proper dilution are quickly absorbed, and will usually have disappeared from the stomach in less than half an hour (Cushny says 20 per cent. absorbed by stomach and 80 per cent. from intestine.) But during a meal an amount of alcohol can be ingested without systemic effects that, if taken before the meal, *i. e.*, on an empty stomach, would produce distinct feelings or manifestations of intoxication. This is a fact that is well known to the laity, and the difference is due to admixture with the food and the consequent retardation of absorption. The effect of alcohol on the absorption of other substances, such as digestive products, water, and drugs, is favorable, unless the alcohol is present in strength great enough to injure the cells of the mucous membrane or to produce a coating of thick mucus, or to act as an astringent, *i. e.*, in a strength above about 20 per cent.

(*b*) *Motility.*—Kast's experiments with alcohol up to 20 per cent. strength indicated increased motility; those of Gluzinski show retarded motility. From an experimental point of view, therefore, the effect on motility remains undecided. Yet, clinically, alcohol seems to increase the motor functions, for solutions containing above 20 per cent. and the distilled liquors, even when diluted to 20 per cent., are prompt and powerful carminatives.

(*c*) *Secretion.*—1. *The Secretion of Saliva and Mucus.*—In the mouth these are increased by strong alcohol, as with other irritants, the resulting secretion being for protective purposes.

In the stomach, also, 50 per cent. alcohol, as in a distilled liquor, quickly results in the secretion of a protecting coat of thick, tenacious mucus. This not only protects the mucous membrane from further injury by the alcohol, but by retarding absorption serves to protect the liver and to lessen the systemic effects.

2. *The Secretion of Gastric Juice.*—We are able to divide the action of alcohol and alcoholic drinks upon this secretion into three distinct periods, viz.:

1. The period of excitation of the taste-buds or olfactory nerves to produce appetite.
2. The period during which the alcohol is in the stomach.
3. The period after absorption while the alcohol is in the circulating blood.

First Period.—Pawlow's work established the fact that

response was more rapid; and this might be because of freedom of the motor areas from the inhibition required in judgment. In some persons some of the depression persisted for from twelve to twenty-four hours. In some there was no depression at all, even from 100 c.c. of alcohol, which would be the amount in a tumblerful of whisky.

Jacoby found that alcohol made a keener perception of differences of weight, but thought this due to slower (more deliberate) cerebration. Some observers have noted a brief period of true stimulation of the perceptive faculties before the general depression supervenes. Many good men have thought that the quicker action in response to a stimulus was due to primary freeing of the motor functions from inhibition.

Alcohol, then, is an intellectual depressant, *i. e.*, a narcotic, and it is a direct antagonist of caffeine. Yet on some particular occasions, or in special kinds of work, the peculiar narcotic effects of alcohol may actually favor better work, for example—(*a*) Where nervousness, or embarrassment, or anxiety cause too great inhibition and prevent unembarrassed thinking, *e. g.*, one who is to speak in public may increase his confidence, lessen his self-consciousness, and set free his thoughts, so that he can speak without embarrassment. (*b*) When the writer of imaginative or emotional literature or poetry is unable to get himself into the imaginative state; a dose of whisky may set free his imaginative powers, so that he can outline his story, any errors of grammar or construction being corrected later. (*c*) When a musician is unable to reach the emotional state necessary to enthuse his hearers, he may find himself able to do so after a drink of whisky, for though he may strike a number of wrong notes, he puts life into his music and thrills his audience. These are not cases of intellectual stimulation, but intellectual depression. Though these things are true in particular instances, I would caution against depending on any such aid, for it is impossible to predict the dose that will just give the desired assistance. Too much alcohol spoils everything, for the inferiority of work produced is not realized by the drinker. Work requiring deduction and keenness of judgment, such as scientific writing or investigation, cannot be done so well under the influence of even small amounts of alcohol.

Sexuality.—From depression of the cerebrum the sexual *desires* are under much less restraint than normal, and Havelock Ellis rightly says: "It is obvious that those who wish to cultivate a strict chastity of thought and feeling would do well to avoid alcohol altogether, or to use it in its lightest forms and in moderation." If much alcohol is taken, the sexual *powers* are impaired

One of Neumann's experiments was as follows: For five days he kept dogs in nitrogen equilibrium (that is, on a mixed diet whose daily nitrogen was the same in amount as the daily excretion of N). He then for four days gave the same diet, but with half its fat omitted; the nitrogen excretion increased, showing that there was more protein destruction, *i. e.*, the proteins were being drawn upon to supply the energy that the fat had supplied. Then alcohol, in amount chemically equivalent to the omitted fat, was added to the food, and the nitrogen equilibrium again became established. Therefore alcohol was able to spare the proteins in the same way as the fat. But Neumann went further, and not only gave the alcohol, but also replaced the omitted fat, and the nitrogen excreted became less than that ingested, *i. e.*, there was less protein destruction than with either alcohol or fat alone, and protein was being stored up, so that alcohol performed the function of fat in sparing protein even when the fat in the food was sufficient. Lastly, Neumann omitted both the fat and the alcohol, and the nitrogen excretion again greatly exceeded that taken in with the food, that is, there was excessive protein destruction. We might sum up the teachings of these experiments as follows: *When fat in the food is deficient, alcohol can entirely compensate for the deficiency, at least for a short period; it yields the energy that fat would yield, and so spares protein and prevents tissue waste. When alcohol and fat are administered together in quantities above the needs of the body, the alcohol is the more easily utilized to supply energy, so that the fat is spared and stored up in the body.*

(In metabolism experiments with alcohol it has been found that there is usually a loss in protein for the first three or four days until tolerance is established; but if the alcohol is begun in very small doses, the primary protein destruction does not occur; and in those accustomed to alcohol, even larger quantities of alcoholic drinks result in no primary nitrogen loss, even in fever. —Ott.)

Can Alcohol Directly Replace Carbohydrates in the Food?—To test this, Atwater and Benedict examined excreta of a man at rest during five-day periods. During the first period he was on a fixed diet, without sugar, representing 2290 absorbable calories. He gained very slightly in weight, the daily calories of metabolism being 2176, and the calories of retention being 77. During the second period he took the same diet plus 72 gm. of alcohol (500 calories), and gained more in weight; the calories of metabolism being 2258 and those of retention 589. During the third period he took the same diet with the exclusion of the alcohol, and the substitution therefor of 130 gm. of sugar (515 calories); the

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tractions, increased amount of work in a given time, and delay of fatigue. In these cases, of course, there was no supply of nutritive material and the alcohol may have served as food.

Human ergographic and dynamometric experiments indicate that small quantities increase the power for muscular work for a short time, but that fatigue sets in more early.

Hellsten (1904) showed that 10 gm. of alcohol given to a non-drinker increased the muscular power for the first half-hour up to 9 per cent., the best work being done during the second period of fifteen minutes; in the third period of fifteen minutes the muscular power decreased to 6 per cent. below normal. After moderate fatigue the primary increase after alcohol was more noticeable. From his experiments he concluded that there was some primary stimulation either of the motor centers or muscle, and that in fatigue, or when nutritive material was lacking, the effect of the alcohol as food enhanced the stimulation. The subsequent decrease in muscular power is essentially due to the depression of the motor centers of brain and cord.

Schnyder and Dubois (1903) compared alcohol with tropon (a protein food). From over 400 ergograph experiments they concluded that alcohol in small quantities has a favorable action on muscular power when it is taken by a fasting person who has to some degree exhausted his reserves by active work. But that because of the central depressant effect the increase in muscular power is below that from an ordinary food substance of the same caloric value; and that, if the individual has already an adequate food-supply, the late depression of muscular power may be the only manifestation of the alcohol.

It is evident from such experiments that any good effects on muscle and work depend not on stimulation, but on nutrition.

Endurance.—Tests with soldiers over a number of days have shown that, in a regiment on the march, provided that all were well fed, those companies which received no alcohol during the day were able to march further or were in better condition at the end of the day than the companies which received alcohol. If they were underfed, those receiving alcohol in the ration could endure the most. As the result of extensive experiments of this kind made by Leistenstorfer, the German Government decided to replace alcoholic stimulants with sugar or sweetened chocolate.

Zuntz and Schumberg made a study on the temperature of marching soldiers, and found that while normally they could carry an average load of 22 kilograms and march 15 to 20 kilometers without noticeable rise in body-temperature, yet from the same work, after a drinking-bout, the temperature rose to from 102.7° F. (39.3° C.) to 105° F. (40.5° C.). Parkes speaks of a

direct stimulant to the heart muscle, and also probably in debilitated persons as energy-supplying food for the heart. In nervous, restless, excited persons it may result in a secondary quieting of the heart through its narcotic effect.

The rate of the heart is quickened, at first because of the reflex effect from the mouth, later possibly because of direct depression of the vagus center or of direct muscular stimulation.

Arteries.—In perfusion of an isolated viscus there is no effect unless the alcohol percentage is above that compatible with life.

Arterial Pressure.—From ordinary amounts there is regularly no change in pressure, but when intoxicating doses are given, there is a slow and very gradual moderate fall. The arterioles are dilated, as shown by the increase in volume of an organ placed in an oncometer. This is due to depression of the vasoconstrictor center, for in an animal with spinal cord severed to cut off central control of the splanchnic arteries the pressure tends to rise.

Brooks, experimenting with unanesthetized animals, found that, about fifteen minutes after alcohol was placed in the stomach through a gastric fistula, there resulted a very gradual fall in pressure that lasted about an hour. When the alcohol was given intravenously in small amounts, there was either no change in pressure, or a slight fall, followed by rapid recovery; from large amounts there was a continuous and gradual fall, with decreased amplitude of the pulse and increased rate.

Though, ordinarily, there is no rise in arterial pressure, the rate of flow, as measured by the stromuhr, is increased (Wood and Hoyt). This means a greater supply of blood to the organs, an effect not appreciated from blood-pressure experiments.

The *cutaneous arterioles* are regularly dilated, even from therapeutic doses, so that the skin is flushed, and there is a feeling of warmth and comfort, and there is a tendency to sweating. In susceptible persons even a teaspoonful of a strongly alcoholic tincture is enough to flush the face or even to give a feeling of light-headedness.

To sum up, the effects upon the circulation are:

1. *Before Absorption.*—Reflex stimulation and rise in arterial pressure from local irritation of the mouth or throat. This is the main action upon the circulation.

2. *After Absorption.*—(*a*) From moderate amounts, slight direct stimulation of the heart muscle and dilatation of the skin vessels; from large amounts, direct depression of the heart muscle. (*b*) Depression of vasoconstrictor center and perhaps of vagus center. (*c*) Acceleration of blood-flow without rise in blood-

pressure. (*d*) Dilatation of the skin vessels. (*e*) In debility it may serve as a source of energy for the heart.

Respiration.—Willmann gave a rabbit a little oil of mustard in 10 c.c. of saline by mouth. There was no effect on respiration, though the stomach mucosa was very red and irritated. He gave a rabbit alcohol, and though the stomach did not show any irritation and did not differ from that of a control, there was great increase in the depth and frequency of respiration. He believed, therefore, that the stimulus was not from irritation of the stomach.

Experiments were also made on human beings by Binz and his pupils. In one case, for example, 75 centiliters of old sherry was given at 8.25 A. M. The respiration rose from 3 to 4.25 liters of air per minute, reached 5 liters at 10.30, then fell again, but was 4 liters at 11.30. The student was somnolent during this time, as he was unaccustomed to wine.

The Effect on Respiration in Fatigue.—A boy of fifteen years, weighing 45 kilos, was given 20 c.c. alcohol plus 12 gm. sugar, a little lemon-juice, and 80 c.c. water. How much effect the sugar would have was not determined. The effects were as follows:

(*a*) When not fatigued —in 10	minutes	after	alcohol	—air	resp.	= + 6.39	per	cent.
40	"	"	"	"	"	= + 2.74	"	"
60	"	"	"	"	"	= − 7.77	"	"
(*b*) When slightly tired—in 10	"	"	"	"	"	= +12.00	"	"
30	"	"	"	"	"	= +11.20	"	"
40	"	"	"	"	"	= + 4.25	"	"
(*c*) When very tired —in 10	"	"	"	"	"	= +26.80	"	"
30	"	"	"	"	"	= +33.19	"	"
40	"	"	"	"	"	= +52.34	"	"

Weissenfeld tested 74 cases, and Wendelstadt, 55. These men, and Zuntz and Bardez, von Jaksch, and Geppert obtained uniformly similar results.

Therefore alcohol during fasting or fatigue causes a considerable increase in respiration, the same increase occurring during sleep. "The increase is apparently central, and is greatest from wines because of their ethers" (Binz).

Loewy's experiments seem to show that there is no increase in the sensitiveness of the center to carbon dioxide, and the exact site of action of alcohol in increasing respiration is not known. In late stages of poisoning the respiratory center becomes greatly depressed.

Temperature.—Through the dilatation of the skin vessels and the sweating, alcohol increases the dissipation of heat, and so tends to lower the temperature. As the skin is the seat of the important temperature nerve-endings, the great amount of

But whether this lessened excretion of uric acid means increased storage in the system, with the ultimate production of a new attack, or lessened formation of uric acid, has not been fully determined. Yet clinical experience favors the view that alcohol may precipitate an attack of gout; and particularly is this true of the malt liquors which contain 0.145 gm. of purin bodies per liter.

Excretion of Sugar.—In diabetes, *medicinal or dietetic amounts* of alcohol apparently have no influence upon the quantity of sugar excreted or upon the course of the disease. Hence distilled liquors, and sometimes the dry wines, are allowed in moderation in this disease. The malt liquors and sweet wines are forbidden because of their carbohydrate ingredients and acids, and not because of their alcohol. In severe diabetes the acids of wine, and probably also the alcohol, are harmful. After large amounts of alcohol, as taken in a debauch, and in chronic alcoholism, glycosuria may appear even in a non-diabetic; and in a diabetic there may be not only increased sugar excretion, but the formation of acetone, diacetic acid, and betaoxybutyric acid, with the development of pronounced acidosis and perhaps fatal diabetic coma. (The writer had a case in which fatal diabetic coma followed the ingestion of a quart of claret.)

Toxicology.—In susceptible people even a teaspoonful of a strongly alcoholic tincture is enough to flush the face and make the head feel light. In unaccustomed animals Grahant found that 6 parts per 1000 in the blood could be recovered from.

Acute poisoning is drunkenness, and we have already considered its cerebral manifestations. The inattention to what is going on, the maudlin intellect, the uncertain speech, the staggering gait, need no description. Alcoholics tend to be pugnacious, lacrymose, sleepy, morose, cheerful, or overpolite, according to their temperaments, or owing to some special action of the liquor. There is some anesthesia, so that the pain of an injury is not felt; and there is partial muscular relaxation, so that falls are less likely than usual to result in broken bones. This stage of intoxication persists for a long time, but eventually passes into that of *stupor*, *i. e.*, deep sleep from which one can be awakened with difficulty. When aroused from this alcoholic stupor, the patient shows stupidity and lack of intelligence, incoherent speech, relaxed muscles, and incoördination, so that he will fall limp, or at least have difficulty in walking. On being left alone he relapses at once into the stuporous sleep. This state distinguishes alcoholism from morphine poisoning, in which the patient on being aroused shows reasonable intelligence,

can speak distinctly and answer questions, and can be kept actively walking.

The stupor of alcoholics often verges closely on coma; but even at this stage it is characteristic of alcohol that pressure on the supra-orbital nerve results in wincing or will actually arouse the patient. In this respect alcoholic stupor or coma differs from that of uremia, diabetes, opium-poisoning, or cerebral injury, in which pressure on the supra-orbital nerve meets with no response. Following the onset of coma, the alcoholic may readily pass into collapse and die. Death is not infrequent also from a fracture of the skull received in a drunken fall, or from pneumonia brought on by exposure. Very large amounts of strong liquor may produce death from reflex shock. Death has frequently occurred from drinking large quantities quickly as the result of a bet.

Treatment.—It is the usual plan to give plenty of fresh air and let the drunkard sleep it off. Occasionally, especially if he has smoked freely, the patient vomits and is much improved. In some cases it may be necessary to wash out the stomach or to catheterize the bladder. Caffeine and strychnine are antidotal. If the patient goes into collapse, the regular treatment for collapse is indicated.

After-effects.—The systemic after-effects resemble those of ether anesthesia; viz., coated tongue, bad taste in mouth, loss of appetite, nausea, retching, vomiting, constipation, headache (bursting head), great restlessness, mental depression (remorse or disgust with one's self), and lack of energy. There are regularly thirst and desire for more liquor. There may be paralysis of an arm (Sunday-morning paralysis), from the drunkard having lain upon the arm in such a way as to cause pressure upon the brachial plexus.

As a rule, the usual morning distress may be treated effectively with aromatic spirits of ammonia, or a hot, bitter, and carminative mixture. This is known as a "pick-me-up" or "morning tonic." There can hardly be any objection to giving teaspoonful doses of an alcoholic tincture even though one is treating alcoholism. A good prescription might be:

℞. Tinct. capsici ..... ʒj (4 c.c.)
Tinct. lavandulæ comp. ..... ℥ss (15 c.c.)
Spiritus ammoniæ aromatici ....q. s. ad ℥ij (60 c.c.)
M. et Sig.—One teaspoonful in water every one or two hours.

If the patient is very restless, bromides may be given, but it must be remembered that it is irrational to give strychnine or [illegible] at the same time. A dose of calomel tends to lessen

the "bilious" feeling; and lavage or a hypodermatic of an emetic dose of apomorphine, repeated, if necessary, will clean the stomach when there is distressing retching and nausea.

Chronic Alcoholism.—Inebriates may, for convenience, be divided into three classes, viz., the steady drinkers, the periodic drinkers, and the dipsomaniacs. The steady drinkers are always under the influence of liquor, though not of necessity intoxicated. The periodic drinkers are those who drink to excess at intervals, being started off on the drinking bout by some small provocation. They have little will power. They soon lose their sense of responsibility, and tend to drink larger and larger quantities, though at first attending to business. Dipsomaniacs are the victims of epileptic insanity (Diefendorf).

In *dipsomania* the impulse to drink is immediate and irresistible. It comes over the victim like a paroxysm. It may occur in persons who hold positions of responsibility; and these, during the attack, may perform ruinous acts of business, commit social offenses, etc. In the intervals the victims may drink temperately or not at all, and there is no fear that the sight of liquor will bring on a paroxysm. In the attack the drinking may last only a day or two, or may continue in gradually increasing quantities, or with partial remissions, for weeks; it frequently terminates in prostration, failure of the patient's stomach, and nervous breakdown. The patients may be unable to remember where they have been or what they have done. A man who had not drunk for some time was left a fortune on condition that he refrained from drink for a year. This acted as the exciting cause of an attack, and within an hour of the reading of the will he was intoxicated (Crothers).

In chronic alcoholism the patient is bleary-eyed and nervous, has a tremor of the hands, lips, and tongue, doesn't care to go to work, smokes to excess, and has a great thirst for liquors. He may have various gastro-intestinal disturbances, disgust for food, nausea, retching, vomiting, constipation; and there may be an alcoholic gastritis, with irritability of the stomach, a secretion of large quantities of thick mucus, and a gastric juice of variable quality, sometimes highly acid and sometimes deficient in acid. There may be a swollen, tender liver. The nervous system is severely upset, and there may be mental depression, anxiety, lack of energy, loss of will-power, and great general nervousness and restlessness. In some cases there is a peripheral neuritis, usually of hands or feet, but sometimes in other parts of the body, with tingling and numbness or acute tenderness.

The patient may display *Korsakoff's psychosis*, which is a condition of disorientation with the memory strikingly at fault.

stantly asleep for from twenty-four to thirty-six hours has its strong advocates, and even the rest obtained from a hypodermatic of morphine sulphate, ¼ grain, and hyoscine bromide, $\frac{1}{100}$ grain, may be of great benefit.

3. *To supply food*, small quantities of hot milk, koumiss, oyster-stew, junket, calves'-foot jelly, etc., may be administered at frequent intervals. As soon as the stomach becomes tolerant, milk-toast, poached egg on toast, oysters, etc., may be allowed.

4. *To promote elimination*, valuable measures are plenty of fresh air, because of excretion of the alcohol by the lungs, sweating by hot baths, or a Turkish bath if patient is able to stand it, and vigorous catharsis with compound cathartic pills, or calomel followed by citrate of magnesia.

Delirium tremens ("the horrors") is a special manifestation of chronic alcoholism. It rarely occurs except after continued heavy drinking, and in such cases may be brought on by the sudden withdrawal of the alcohol or by a temporary great excess, or by pneumonia or by traumatism, *e. g.*, fracture of a limb. It is characterized by horrible hallucinations of sight and hearing. The hallucinations take the form of snakes, rats, things crawling over the body, or people with harmful intentions. The patient sees them coming or hears voices. He shows intense activity, talking, muttering, crying out, attempting to get out of bed, or perhaps to escape from the attendants. Insomnia is almost complete, and there may be a temperature of 102° or 103° F. Death is quite a frequent outcome, resulting usually either from pneumonia, from traumatism, or from collapse brought on by the alcoholic depression and the excessive activity or struggling.

The *treatment* is that for chronic alcoholism, and in addition wise restraint and close watching of the circulation because of the tendency to collapse. The withdrawal of liquor must be managed more deliberately. In a study of the treatment in 500 cases Ranson (1909) found ergot apparently the best remedy. The mortality in those getting ergot was 21.6 per cent. below the average.

Late in the course of lobar pneumonia in persons accustomed to much alcohol there is sometimes seen a peculiar maniacal delirium verging on delirium tremens. In such cases the delirium may not yield until good-sized doses of whisky or brandy are administered.

The **cure of the habit** depends on the patient's desire for cure, on the temperament of the patient, and on the type of the drinker. From a therapeutic point of view inebriates may be classed as: those who do not have an irresistible craving for alcohol, and those who do have the craving (Crothers). The

Rubin found that a hypodermatic of alcohol, ether, or chloroform would render rabbits more susceptible to streptococcus and pneumococcus infections; Stewart, that a small amount of alcohol lowers the opsonic index to the bacillus tuberculosis and streptococcus, and Graham that animals given alcohol or ether succumb more readily to experimental infection than controls, especially in those diseases of which the immunity is chiefly phagocytic.

Alcohol in mildly intoxicating quantities for several days after the injection of the antigen retards the formation of the antibodies (Müller, 1904; Wirgin, 1905); but the results of others' experiments seem to indicate a favorable action in the formation of antibodies from a single mildly toxic dose of alcohol at or near the time the antigen is introduced. Laitinen found it difficult to immunize alcoholized animals to diphtheria toxin. Parkinson found that a small dose in rabbits might stimulate the production of antibodies temporarily and that it lessened the reacting mechanism to vaccines; that a large dose will lower the opsonic index for twenty-four hours, and that continued moderate doses cause a permanent lowering of the opsonic index. It has no action on phagocytic activity if present in a strength below 12.5 per cent.

Preventives.—Leonard Hill reports that in alcohol poisoning fatty infiltration of the liver is prevented by feeding glycogen-builders, *i. e.*, carbohydrates. Dogs which on pure fat diet put on 25 per cent. of dry liver substance as fat, have this per cent. lowered to one-half or less by the feeding of glycogen-builders at the same time. Von Noorden noted that the percentage of fat in both heart and liver of starved dogs increases in a few days from alcohol, but that this effect is prevented by sugar. Similar though less marked protection of the liver has been reported from sodium bicarbonate.

Therapeutics.—*External.*—As *antiseptic*, as in cleansing surgeon's hands or skin of patient. As *cooling lotion* in headache or in itching or for bruises (eau de cologne, spirit of camphor, witch-hazel, or tincture of arnica). For rubbing the body of an invalid, 50 to 95 per cent. alcohol is very refreshing, and in fever is cooling. As *anidrotic* in sweating of the hands and feet and in the night-sweats of tuberculosis. *To harden the skin*, as when bed-sores are threatened. In *refractory trigeminal neuralgia*, 15 minims (1 c.c.) may be injected into the nerve.

As a *preventive of carbolic-acid burns*, alcohol is the best remedy. Its affinity for the phenol being greater than that of the tissues, it prevents penetration of the carbolic. When the carbolic is swallowed, alcohol is best given in the form of whisky, but it

1. *Respiration.*—(*a*) The number per minute remains unaltered; the movement becomes shallow and thoracic in type; (*b*) the amount of inspired air per minute is lessened by from one-half to two-thirds; (*c*) the output of CO_2 is diminished by one-half to two-thirds.

2. *Circulation.*—(*a*) The blood congests in the limbs; (*b*) the venous system is engorged; (*c*) the arterial pressure falls; (*d*) the pulse-rate diminishes; and (*e*) the velocity of blood-flow decreases.

3. *Temperature.*—The temperature falls during the night. The production of heat is estimated to diminish by from one-half to two-thirds.

4. *Nervous System.*—(*a*) The blood-flow through the brain is diminished; (*b*) the acidity of the cortex decreases; (*c*) the excitability of consciousness to external stimuli steadily decreases during the first one to two hours of sound sleep. After that period the excitability rapidly becomes almost as great as it is toward the end of sleep; and (*d*) consciousness alone seems to be abrogated during sleep. The nerves and the special senses continue to transmit impulses and produce reflex movements.

Verworn's Theory.—Sleep, as pointed out by Verworn, is entirely different from narcosis. Sleep comes because of—(1) The lessened irritability, *i. e.*, fatigue, of the cells of the cerebral cortex which results from work; and (2) the removal of external stimuli, as noise, lights, etc. Narcosis comes from direct and deliberate depression of the cells of the cerebral cortex. In sleep the cells recover from fatigue, regain their lost irritability, and are restored to their full capacity for work; in other words, sleep implies restitution. In narcosis, on the other hand, there is no restitution, and the cells lose their irritability and go through the stages of fatigue production. A narcotic is prone to be followed by sleep because it produces fatigue of the cells, and when a narcotic substance is given to produce sleep (*i. e.*, a hypnotic), it does so by depressing the cells and thus reducing the excitability of the cerebral cortex which is preventing sleep. The depression of the cells thus produced may then be followed by restorative sleep, but the hypnotic does not directly or primarily induce natural sleep.

If too much of the hypnotic is given, the primary narcosis is not followed by restorative sleep, but continues for a long time, and results in fatigue of the cerebral cells instead of restoration. This effect is sometimes seen during the following day, especially in old people, and it shows in mental and physical depression and tiredness.

Hypnotic measures include drugs, hot baths, the establishment of proper conditions for sleeping, etc. They promote sleep, either

effect are irritant, and unless well diluted may induce nausea and even vomiting.

Absorption is fairly rapid from the stomach and intestines.

Nervous System.—In hypnotic doses chloral hydrate fairly rapidly induces a mild but prolonged cerebral depression, accompanied by the phenomena of natural sleep, and it is a very reliable hypnotic. The pulse and respiration are somewhat slowed, the pupil is in midcontraction, the CO_2 of the blood is reduced, as in sleep, and the patient may be fairly easily aroused by noises or pain or other sleep antagonists.

From *therapeutic amounts* there is no essential analgesia, so that pain is not abolished, and in animal experiments it is found that there must be profound narcosis before there is any perceptible diminution in the response to painful stimuli. The reflexes are somewhat depressed, but not enough by safe amounts to make the drug more than weakly antidotal to the convulsions of eclampsia, tetanus, and strychnine poisoning. In dogs chloral is antidotal to strychnine, for dogs can take a much larger dose of chloral without dangerous depression. Pringard gave 0.25 gm., and Hopkins 1.5 gm., per kilo without death.

From *poisonous doses* there is profound stupor, diminished excitability of the motor areas of the brain, as shown in experiments with dogs, depressed pain sense, and diminished reflexes, so that there is more or less muscular relaxation. The patient passes through stages similar to those from chloroform, and may pass to a state of surgical anesthesia (coma), with abolition of consciousness and of the reflexes, but in imminent danger of collapse.

The peripheral nerves are not affected by systemic administration. From local application there is slight depression of the sensory nerve-endings. (See Local Action.)

Respiration.—In the sleep produced by therapeutic doses the breathing is slowed as in ordinary sleep; while from poisonous doses, through depression of the respiratory center and the failure of the circulation, the breathing becomes slow and shallow. Death takes place usually from failure of the respiration, but restoration by artificial respiration is impossible because of the feeble circulation.

Circulation.—The addition of chloral hydrate to the fluid used in perfusing an isolated heart induces a few strengthened beats, presumably from protoplasmic irritation, and then a slowing of the heart, with gradually weakening contraction in systole and increasing relaxation in diastole. The heart loses its tone and its contractility, and soon stops with the ventricles widely

Administration.—In aqueous solution, well diluted, often with the addition of bromides. It should never be given with alcohol (whisky, elixirs, etc.), as the chloral alcoholate formed is rapidly depressing to the cerebrum and medulla and constitutes the notorious "knock-out drops."

Butyl chloral hydrate is sometimes employed for trifacial neuralgia in dose of 5 grains (0.3 gm.).

Chloralformamidum (chloralamide) ($CCl_3COH.HCONH_2$) is a crystalline compound of chloral and formamide ($HCONH_2$), which splits into its components in the blood. Its hypnotic action, therefore, results from chloral, but the formamide is believed to render it less depressing to the heart and vasoconstrictor center. In spite of the formamide, however, the chloral set free has its usual metabolic effects. Chloralamide is soluble in 18.7 parts of water and 1.3 of alcohol. Heated with water to 60° C. (140° F.), it is separated into its components. The dose for mild hypnosis is 15 to 30 grains, administered in capsule, cachet, or powder, or in hot whisky. An elixir is on the market. It does not form knock-out drops.

Chloretone, chlor-butanol, or chloroform-acetone, $CCl_3C.(CH_3)_2.OH$, is a compound of acetone and chloroform. It is a white powder, soluble in hot water, alcohol, glycerin, and the fixed and volatile oils. It is somewhat antiseptic, and is used as a preservative in solutions of adrenaline and other unstable bodies. Its solutions are not absorbed by the unbroken skin, but are absorbed by mucous membranes and raw surfaces, and are locally somewhat anesthetic, depressing the ends of the sensory nerves. On this account it may be used in solution or powder, as an antiseptic, analgesic application to ulcers, as of the leg or stomach, or in tuberculous laryngitis or in a decayed tooth. In seasickness it acts both locally in the stomach, to lessen nausea and vomiting, and as a central sedative. Systemically it depresses the cerebrum, producing quiet and sleep. But it is a much less powerful hypnotic than chloral, and is said to be not without danger in the larger doses. It has been recommended for its narcotic value as a preliminary to ether anesthesia. Dose, 15 grains (1 gm.).

In the laboratory it is employed to anesthetize small animals, such as rabbits, but a systemic effect sufficient to abolish pain cannot be elicited in man without danger.

ETHYLATED COMPOUNDS

In experimental chemistry it has been found that the introduction of the radicle *ethyl*, C_2H_5, into an organic chemical will frequently confer upon it a sedative action. Hence many synthetic hypnotics containing ethyl groups have been placed upon

day. In some cases the sleep is dreamy, unrefreshing; and at times, particularly in old people, sleep persists for twenty-four to thirty-six hours. Itching of the skin, erythema and other skin rashes, conjunctivitis, and glycosuria have been reported following its use. It is extensively employed as a hypnotic in all ordinary conditions where sleep is wanting. It is also used to some extent in epilepsy, delirium tremens, prolonged labor, and the vomiting of pregnancy and seasickness. Dose, 5 grains (0.3 gm.). A sodium compound of veronal, soluble in 5 parts of water, has been marketed under the names Medinal and Veronal-sodium. It is bitter, but may be used by rectum, or even in 10 per cent. solution, hypodermatically.

Toxicology.—Jacobi says that it causes relaxation of the capillary walls similar to that from arsenic, with fall in blood-pressure, congestion of the abdominal viscera, and depression of respiration, in addition to the hypnotic action. It does not affect the cardiac muscle. The average lethal dose is 8 to 10 gm. The treatment is for collapse. Several deaths have been reported.

Bromural, monobrom-valeryl-urea, $(CH_3)_2CH.CHBr.CONH.CO.NH_2$., resembles veronal very closely in its effects but is less active. Dose, 15 grains (1 gm.).

Adalin, brom-di-ethyl-acetyl-carbamide, $C(C_2H_5)_2Br.CONH.CONH_2$, is a substance of the same class as veronal and bromural. It is soluble freely in alcohol, but with difficulty in water, is almost tasteless, and is milder in action than veronal. Dose, 15 grains (1 gm.).

Urethane, æthylis carbamas, $NH_2COOC_2H_5$, soluble in less than its own weight of water, is a mild hypnotic and diuretic in dose of 1 dram (4 gm.). It changes in the body to urea, and because of this fact is advised against in nephritis.

Hedonal is methyl-propyl-carbinol-urethane, soluble in 120 parts of water and readily in alcohol. It is incompatible with alkalies. Dose, 15 grains (1 gm.). It has been used as an intravenous anesthetic, Fedoroff (1910) reporting 330 cases. Page (1912) recommends a solution of 0.75 per cent. in normal saline infused at the rate of 50 to 150 c.c. per minute. The adult dose is 500 c.c. The respiration was deep and regular, the pulse good, the reflexes were abolished. Veale (1912) employed it in quantities up to 1200 c.c., and from the larger amounts got skin edema, pulmonary edema, bronchitis, and pneumonia, as well as thrombosis in the vein.

Paraldehyd $(CH_3COH)_3$ is not an ethylated compound, but may be considered here. It is a volatile liquid with a penetrating, disagreeable ethereal odor and a burning taste. It is soluble in

7. *To quiet the reflexes* (lessen the heightened tone) in spastic conditions due to lesions of the motor tract, as in multiple sclerosis.

8. *To lessen cardiac excitability*, as in extrasystoles and paroxysmal tachycardia—doses of 2 to 3 drams (8–12 gm.).

Of the various bromides, the potassium and sodium salts, in ordinary doses, have no measurable differences, and are preferred to the others. In the very large doses the potassium radicle may have a special depressing effect upon the muscle of the heart and arteries. The belief that ammonium bromide is less depressing to the heart than the other bromides is not justified. (See Ammonium Chloride.)

Bromipin is a combination of bromine with oil of sesame, and may be given in the form of an emulsion. It is said to be free from irritating effects upon the stomach, and is sometimes substituted for the alkaline bromides when there is gastric irritability. It is of two strengths, 10 and 25 per cent., and the dose is 1 to 2 drams (4–8 c.c.) made into an emulsion. In epilepsy Kothe recommends 75 grains (5 gm.) three times a day, increasing up to 600 grains (40 gm.).

Bromoform ($CHBr_3$) is a homologue of chloroform, $CHCl_3$. It is a heavy liquid, readily soluble in alcohol, very slightly soluble in water, and sweet to the taste. It is very limpid, so that 1 minim contains about 5 or 6 drops. Its only therapeutic use is in the treatment of whooping-cough. The dose, 3 drops, or ½ minim (0.03 c.c.) for a child one year old, or 5 minims (0.3 c.c.) for an adult, is usually given suspended in syrup, but is better dissolved in alcohol or oil. Poisoning has occurred a number of times from the undissolved bromoform at the bottom of a bottle, so it should be well shaken before the dose is poured out. Serious narcosis and collapse are reported in a child of eighteen months from a dose of 8 drops.

OPIUM

Opium is the "concrete milky exudation obtained by incising the unripe capsules of *Papaver somniferum* (Fam. *Papaveraceæ*), and yielding, in its normal moist condition, not less than 9 per cent. of morphine." It is simply the dried milk-juice which exudes from two or three encircling incisions made in the green poppy capsules of the common poppy as grown in oriental countries. The only opium that meets the U. S. P. requirements is that from Asia Minor, known as Turkish or Smyrna opium. That used for smoking is less strong and comes mostly from India and China.

Opium is expensive and is much adulterated with vegetable débris, sand, earth, and even nails and bullets to increase its

constrictor, and pupil-contracting centers are stimulated, while the respiratory, the cough, the temperature-regulating, and the secretory centers lose their sensitiveness.

Peripheral Nerves.—There is no effect, though skin sensitiveness is diminished because of diminished perception of stimuli.

The Eye.—After good-sized therapeutic doses, or sometimes after the habitual doses of a morphine devotee, the pupils become contracted. In marked poisoning the contraction is extreme and makes the so-called "pin-point" pupils which are characteristic of opium poisoning. After a lethal dose the pupil, owing to asphyxia, very widely dilates a short time before death, so that after death from morphine poisoning the pupils are found to be dilated. In animals like the cat, in which there is stimulation of the cerebrum, morphine dilates the pupil from the beginning.

Morphine solution dropped in the eye, or injected into an enucleated eyeball (as of an ox), has no effect upon the pupil, so its action is not local or peripheral. It also does not affect the eye through the third nerve ganglia or the cervical ganglia, therefore its action must be purely central. That it stimulates the pupil-contracting center rather than depresses the pupil-dilating center is evident, because paralysis of the latter will not result in pin-point pupils, or produce the wide dilatation of the late stage of poisoning. This late dilatation is probably entirely the result of asphyxia.

The Secretions.—From depression of the secretory center almost all the secretions are diminished, but this is a minor effect in therapeutics. The sweat is increased, but not markedly so, unless the drug is given with a copious hot drink. In health the urine is not essentially changed; but in nephritis it is believed by some writers to be decreased. A satisfactory explanation of this is not forthcoming.

Metabolism.—The quiet and the depressed respiration result in lessened tissue-waste and decreased oxidation. The glycogen of the liver may disappear, and increased lactic acid and sugar appear in the blood, the hyperglycemia sometimes resulting in glycosuria.

Temperature.—In poisoning the fall of temperature may be as much as 2 degrees; and since 80 per cent. of the fall is due to diminished production of heat, and only a slight amount to increased heat dissipation, the drop in temperature must result from the bodily quiet, rather than from the dilatation of the cutaneous vessels and sweating. Morphine is not employed in therapeutics as an antipyretic. The author has seen fever of 102.6° F. with a skin rash and sickness of three or four days follow a single dose of morphine, the patient reporting that this

hyoscyamine, into which it separates when dissolved in water. Hyoscyamine is levo-hyoscyamine, and is readily changed to dextro-hyoscyamine. In the growing belladonna the hyoscyamine is said to form in the young leaves, to be later changed to atropine.

According to the predominance of one or other of these alkaloids, and to the amounts present, the drugs of this group fall into a regular pharmacologic series, as follows:

1. *Belladonna* (root and leaves) —the leaves contain 0.35 per cent., and the root, 0.5 per cent., of alkaloid, which is nearly all atropine. It has, therefore, a typical atropine action.
2. *Scopola* (root) contains 0.5 per cent. of alkaloid, about equally hyoscyamine and atropine. It acts like belladonna, but with somewhat less strength.
3. *Stramonium* (leaves) contains 0.35 per cent. of alkaloid, mostly hyoscyamine, but with small amounts of atropine and hyoscine. It is less stimulating to the cerebrum and may be narcotic.
4. *Hyoscyamus* (leaves) contains 0.08 per cent. of alkaloid, mostly hyoscyamine, with a fair amount of hyoscine, and only traces of atropine. It is rather narcotic, but is weaker than the other drugs of the group.

Fig. 42.—Datura stramonium, *Linné* —flowering branch (Maisch).

Fig. 43.—Capsule of stramonium (thornapple or jimson weed). The seeds have frequently been the cause of poisoning (Bastin).

Preparations and Doses.—The dose of belladonna, scopola,

the usual inhibitory vagus control—an effect that is striking but short-lived.

Atropine depresses primarily these nerve-endings, whether it is applied locally or given internally, while it has no effect at all upon most protoplasmic structures. It is, therefore, a highly selective drug. In speaking thus of nerve-endings from a practical point of view, it should be noted that atropine acts on muscle after nerve degeneration, though not on the contractile substance of the muscle; hence it probably affects some material which acts as the receptor of the nerve impulse. It is some part of the neuromuscular junction, though we speak of it crudely as the nerve-ending.

Absorption and Local Action.—There is slight absorption from plasters, and fair absorption from oily and alcoholic preparations, as ointments and liniments; so the drug may have an effect through the skin on sensory and secretory nerve-endings. In tests with 66 belladonna and scopola plasters Bastedo and Martin (1901) found that these had distinctly more power to stop pain than had the simple plaster without belladonna. That there is some absorption from plasters is shown further by the occasional occurrence of poisoning from them. (See Fig. 47.) Absorption is ready through mucous membranes, the drug rapidly disappearing from stomach and duodenum.

Alimentary Tract.—The chief effects of the drug are to lessen secretion and overcome colic (spasmodic contraction with pain). The taste is bitter.

(*a*) *Secretion.*—After atropine, stimulation of the chorda tympani results in no secretion of saliva. This is not due to the paralysis of the center or ganglia, for stimulation of the nerve peripheral to the ganglia still produces no secretion. Stimulation of the sympathetic, however, continues to cause secretion and vasodilatation, hence there is no paralysis of the secreting cells themselves or of the vasodilating fibers. Therefore the paralyzed portion is the connection between the nerve and the secreting cell, *i. e.*, the nerve-ending. There is some evidence that in large amounts atropine slightly depresses the secretory cells themselves.

In the mouth the saliva and mucous secretions are lessened, and the throat and mouth become dry, an effect which is often noticed from quite small doses. If marked, the patient cannot swallow, though he may be very thirsty. The stomach secretion is less affected, but is probably moderately diminished. Riegel states that this is especially true of the acid portion of the gastric juice.

The *intestinal secretions* tend to be lessened.

Fig. 44.—Longitudinal muscle of small intestine immersed in saline. Tone waves are set up. The addition of 0.1 mg. sulphate at A results in tetanic contraction (cramp), which is abolished by the addition at B of 1 mg. of atropine sulphate. The waves are restored, but not the tone waves. (Tracing made by Dr. C. C. Lieb.)

Arteries.—The vasoconstrictor center is slightly stimulated, and this, with the increased rate of the heart, causes a rise in arterial pressure. This is easily demonstrated in a dog. The contraction of the arteries is most marked in the splanchnic area. In man, however, the rise in blood-pressure from even maximal therapeutic doses is usually inappreciable. In poisoning the vasoconstrictor center tends to be depressed.

The Cutaneous Arterioles.—From poisonous amounts the arteries of the skin, especially those of the head and neck, are dilated; and a flushed face or an erythematous rash like that of scarlet fever is characteristic of atropine poisoning. The flushed skin is from a central action, as there is no flushing if the sympathetic in the neck is divided.

Respiration.—A dose of atropine is followed by deeper and more rapid breathing and a considerable increase in the amount of air inspired. This is largely due to stimulation of the respiratory center; but since the increase is not so great when the afferent vagus fibers from the lungs are cut, there must also be some peripheral action. This is probably depression of the sensory ends of the vagi in the bronchi, for stimuli through these usually slow respiration.

The drug is much used in narcotic poisoning, especially that from morphine. Vollmer (1892) reported that a dog inspiring 4500 c.c. of air per minute was given 0.06 gm. morphine sulphate at 8.45. At 3.40 the air inspiration was 4000 c.c. Then atropine 0.003 gm. was given, and in fourteen minutes the inspiration was 6000 c.c.; in twenty-one minutes, 10,000 c.c. But excessive doses exhaust the center, and must be guarded against in the use of the drug as an antidote. Exhaustion of the center is the cause of death.

The secretions of nose, throat, and bronchi are diminished, so that the membranes are dry and the mucus thick and tenacious. Excessive contraction of the bronchial muscles, as in spasmodic asthma, is overcome by depression of the bronchomotor vagal nerve-endings.

Cerebrum.—The effect from therapeutic doses is very little, but after poisonous amounts there is *psychic* stimulation, and the patient becomes talkative and wakeful, without any pronounced intellectual stimulation like that from caffeine. The poisoning may go on to a delirium, usually of cheerful, loquacious type, and may even result in maniacal excitement. Cerebral depression does not generally ensue until the centers have become exhausted, and then there may follow mental confusion and narcosis leading to sleep, stupor, and coma. In therapeutic amounts the drug is not a narcotic.

animal direct stimulation of the circular muscle results in contraction; therefore the site of the paralyzing action of the drug must be confined to the third-nerve endings or the neuromuscular junction.

The dilatation from atropine is, therefore, the result of the unopposed action of the radial muscles. It is, however, frequently strong enough to break weak adhesions between cornea and iris, or to make an iris which is strongly attached at two points bow out between the points of attachment. The pupil gradually regains its power, but is not fully restored to normal for one or two weeks.

That there is no stimulation of the radial mechanism is evi-

Fig. 46.—Increased convexity of the lens during accommodation. The solid white outline of the lens, *l*, shows its form when relaxed. The dotted line shows the increased curvature of the anterior surface during accommodation, and its advancement forward into the anterior chamber, *a*. *s* is the suspensory ligament; *m*, the ciliary muscle; and *i*, the iris (Landolt).

dent, for, after atropine, stimulation of the cervical sympathetic results in a still greater dilatation; and, in addition, after removal of the superior cervical ganglion and the subsequent degeneration of the sympathetic nerve-fibers, atropine fails to dilate the pupil.

A drug which causes dilatation of the pupil is called a *mydriatic*. Belladonna gets its name from this mydriatic action (*bella*, beautiful; *donna*, lady), which makes the eye seem bright and sparkling.

(*b*) *Accommodation* depends essentially on the curvature of the crystalline lens, and this curvature is regulated by the ciliary muscle. When the ciliary muscle contracts, the capsule of the lens relaxes, and the elastic lens bulges forward and be-

1. *Of mucus*—as in excessive secretion from nose, throat, and bronchi. In bronchitis, in the free running stage of cold in the head, the rhinitis tablets, one every hour for 6 doses, are favorites. Their formula is ½ grain each of camphor and quinine sulphate or bisulphate, and ¼ minim of fluid-extract of belladonna. They are often employed in half this strength.
2. *Of sweat*—as the liniment of belladonna in sweating of hands and feet, and atropine internally for the night-sweats of tuberculosis.
3. *Of milk*—when excessive, or when it is desired to dry up the breasts—liniment or ointment externally; or the drug internally.
4. *Of saliva*—as in profuse salivation from any cause—the drug internally.
5. *Of gastric juice*—as in hyperacidity and hypersecretion, $\frac{1}{400}$ grain atropine sulphate or $\frac{1}{12}$ grain extract of belladonna fifteen or twenty minutes before meals.

B. *To relax overcontracted smooth muscle*—as in spasmodic asthma and spasm of smooth muscle (colic). The latter occurs in the esophagus, cardia (cardiospasm), pylorus (pylorospasm), ileocecal valve, or any part of the stomach or intestine, in the bile-passages (biliary colic), in the pelvis or ureter of the kidney (renal colic), in the neck of the bladder, and in spasmodic dysmenorrhea (in this last mentioned the drug may be of little use because of the congestive condition). Atropine or extract of belladonna may be added to irritant cathartics as a corrective to prevent griping.

In the obstipation which occurs in lead-poisoning and in local peritoneal irritation (as in appendicitis, salpingitis, or ovaritis, or renal or biliary colic) atropine may overcome the reflex spasm with resultant catharsis. In intestinal obstruction from suspected spasm, or in fecal impaction, a large dose, $\frac{1}{13}$ grain (0.005 gm.), has been recommended. But when there is a real surgical obstruction, such a procedure serves only to delay operation, and sometimes with fatal result.

C. *To depress the sensory nerve-endings*—to allay itching (the liniment); to lessen pain, as in ulcer of the leg, anal fissure, or projecting hemorrhoids (the ointment); and the drug by mouth for irritable bladder or urethra, as in cystitis and urethritis, and in enuresis nocturna.

D. *In the eye*—as a mydriatic, cycloplegic, and analgesic, for the following purposes:

1. To facilitate examination of the internal eye posterior to the pupil.

without atropine 75 per cent. died, and with atropine only 28 per cent. died.

All the drugs of the group, viz., belladonna, scopola, stramonium, and hyoscyamus, have actions of the atropine type, and can be used interchangeably for the ordinary peripheral effects.

A special use of the stramonium leaves is in spasmodic asthma, in which condition smoke of the burning leaves is inhaled. The leaves may be burned in a saucer, either alone or with other drugs, or impregnated with potassium nitrate (that is, saturated with a solution of potassium nitrate and then dried); or they may be added to tobacco, lobelia, or cubebs, and made into cigars or cigarettes to be smoked at the time of the attack. The leaves of belladonna will serve as well as those of stramonium.

The chief use of hyoscyamus is as a sedative in irritable bladder, cystitis, and gonorrhea, and as a corrective addition to irritant cathartic pills. It has no advantages over belladonna and is much weaker.

Hyoscyamine (levo-hyoscyamine) is similar in action to atropine, which is a mixture of levo- and dextro-hyoscyamine. Cushny finds that though it acts upon the central nervous system with the same intensity as atropine, it is nearly twice as powerful in its effects upon nerve-endings, especially those of the chorda tympani, of the third nerve in the eye, and of the vagus. It is not readily obtained pure, and is little employed in medicine. Dose of its salts, $\frac{1}{100}$ grain (0.0004 gm.).

Hyoscine or **scopolamine** acts peripherally like atropine, and therefore will allay pain, will dilate the pupil, and will check secretion. But its action in the eye is more rapid and more powerful, a 1 : 500 solution dilating the pupil in ten to thirty minutes, and quickly thereafter paralyzing accommodation, while the effect passes fully away in three to five days. Centrally it differs from atropine in that the period of cerebral stimulation is short and is followed by prolonged mild depression of the psychic and motor centers—that is, the drug is narcotic. In excitable states, as in delirium or mania, it seems to have great power to lessen restlessness or excessive motor activity. Its use is not without danger, however, for it shows early depression of the respiratory and vasoconstrictor centers, and in a great number of instances has caused collapse. Eshner and O'Hara report cases of collapse after $\frac{1}{100}$ grain (0.0006 gm.) of the bromide. The writer has seen fatal collapse from $\frac{1}{50}$ grain (0.0012 gm.) in an alcoholic man with pneumonia; and collapse with recovery from $\frac{1}{25}$ grain (0.0025 gm.) in an alcoholic woman verging on delirium tremens. In both of these the hyoscine had been preceded by ¼ grain (0.015 gm.) of morphine

sulphate. Collapse is reported from the use of the drug in the eye.

Its chief uses are:

1. As narcotic in the insomnia and excitement of acute mania, in delirium tremens, in the delirium of pneumonia (especially in alcoholics), and in the insomnia of alcoholism.

2. As a narcotic and peripheral sedative in treating the morphine and alcoholic habits.

3. As an anaphrodisiac.

4. As a mydriatic and cycloplegic—one drop of a 1 : 500 solution every fifteen minutes for four to six drops.

5. As a general anesthetic or as a preliminary to general anesthesia.

Scopolamine-morphine Anesthesia.—Under the name scopolamine, hyoscine has been employed quite extensively in conjunction with morphine, and it must be considered in its use—(*a*) as an anesthetic, and (*b*) as a preliminary to general anesthesia. *As an anesthetic*, about $\frac{1}{200}$ grain (0.0003 gm.) of scopolamine bromide and ⅛ grain (0.008 gm.) of morphine sulphate are injected two and one-half hours, one and one-half hours, and one-half hour before the operation. This quite frequently results in the abolition of pain. Many authors have spoken well of this method of anesthesia in obstetrics and surgery; but in 69 per cent. of 1988 cases gathered from the literature by Wood, the anesthesia proved unsatisfactory, and in a number of instances had to be supplemented by ether. In addition, though the cases were in general less serious than the average ether case, there were 9 deaths which could beyond reasonable doubt be attributed to the drug, *i. e.*, 1 in 221. Staffen reported its use in 320 obstetric cases, and concluded that the desired results were not obtained, that it was dangerous to mother and child, and that it necessitated close watching of the patient, because of the possibility of nausea, vomiting, excitement, delirium, or collapse. There are many reports, both favorable and unfavorable, a great many considering it inefficient and dangerous as a general anesthetic.

As a preliminary to general anesthesia with ether, a single dose of the mixture of hyoscine and morphine is quite generally recommended by a number of writers, for it promotes a tranquil, drowsy state of the mind which favors anesthesia, it lessens the amount of ether required, and it diminishes the throat and bronchial secretions.

Homatropine bromide (U. S. P.) is the bromide of an artificial alkaloid allied to atropine (it is made by the condensation of tropine and oxytoluic or mandelic acid). It is soluble in 5.7 parts of water, and is used solely for its ocular effects, one drop

of the 1 per cent. solution being dropped in the eye every fifteen minutes for 4 to 6 drops. Dilatation of the pupil comes on quickly, reaches its maximum in one to two hours, and is followed very soon by paralysis of accommodation. The restoration of the accommodation to normal occurs in twenty-four hours, and full restoration of the pupil in forty-eight to seventy-two hours—*i. e.*, much more quickly than after atropine.

Homatropine is, therefore, preferred to atropine for fitting glasses and in ophthalmoscopic examinations; while atropine is preferred where continuous mydriasis is desired, as in inflammatory conditions of the eyeball. Physostigmine will hasten the restoration of the eye.

Euphthalmine has the same relation to eucaine that homatropine bears to tropacocaine. One or two drops of a 5 per cent. solution of the chloride will rapidly dilate the pupil without paralyzing the accommodation. It is of no use in fitting glasses, though it may be employed to examine the posterior eye.

ANIDROTICS

An anidrotic (anhydrotic) is a remedy which tends to reduce sweating. For local sweating, as of the hands and feet, alcohol, eau de cologne, spirit of camphor, and belladonna liniment are favorites. For odorous perspiration of the feet alcohol may be used as a wash, and a mixture of boric and salicylic acids placed in the shoes or stockings.

The chief use of a general anidrotic is in the night-sweats of tuberculosis. (See discussion under Antipyretics and Diaphoretics.) The anidrotic measure may be a hot bath on going to bed, or a body sponge with alcohol, vinegar (or acetic acid), or a solution of alum; or it may be a drug taken internally. Atropine is our most powerful anidrotic. It has the advantage of stimulating respiration, but it has the undesirable effects of drying the throat and increasing the cough, and may even dilate the pupil. In very extensive tests the author found that for internal administration the best general anidrotic is agaricin. Strychnine is also of value. Ergot, which has been highly recommended, seemed to have no effect at all.

Agaricin is an unofficial extract obtained from the fungus, *Polyporus albus*, which grows on the European larch. It is really an impure form of the crystalline principle, *agaric acid*. Its dose is $\frac{1}{10}$ grain (0.006 gm.). In this dose it strongly depresses the ends of the secretory nerves of the sweat-glands, has no undesirable side-effects, and is strongly anidrotic; but its effects are not lasting, so it must be given within four or five

hours of the expected sweat. If the sweat comes on toward morning, the dose may have to be repeated once in the night. In larger doses it sometimes induces nausea, vomiting, diarrhea, and perhaps dryness of the throat, but it does not dilate the pupil. Doses large enough to produce nausea do not give the anidrotic action.

Camphoric acid, $C_8H_{14}(COOH)_2$, is an oxidation product of camphor. It is soluble in alcohol and the fixed oils, and slightly in water. Its dose is 15 grains (1 gm.), given in cachet or powder. Its taste is disagreeable, and its systemic action is mildly that of camphor; but practically its sole use in medicine depends upon its anidrotic property. Roth (1911) found it to be without any direct effect upon the sweat-glands, and was disposed to attribute its action in the night-sweats of tuberculosis to stimulation of the respiratory center.

COCA

Coca is the dried leaves of *Erythroxylon coca*, or of *Erythroxylon truxillense* (Fam. *Erythroxylaceæ*), yielding, when assayed, not less than 0.5 per cent. of its ether-soluble alkaloids. The coca shrub is extensively cultivated at an elevation of 3500 to 6000 feet in the mountains of Peru, Bolivia, and Ecuador, and to some extent also in Mexico and the East and West Indies. It has been estimated that 100,000,000 pounds of the leaves are used annually in South America.

Constituents.—Cocaine and several other alkaloids, all compounds of ecgonine. Cocaine is the methyl-benzoic acid compound; cinnamyl-cocaine is the cinnamic acid compound, and truxilline is the truxillic acid compound.

Preparations and Doses.—

Coca, 0.5 per cent. alkaloid, 30 grains (2 gm.).

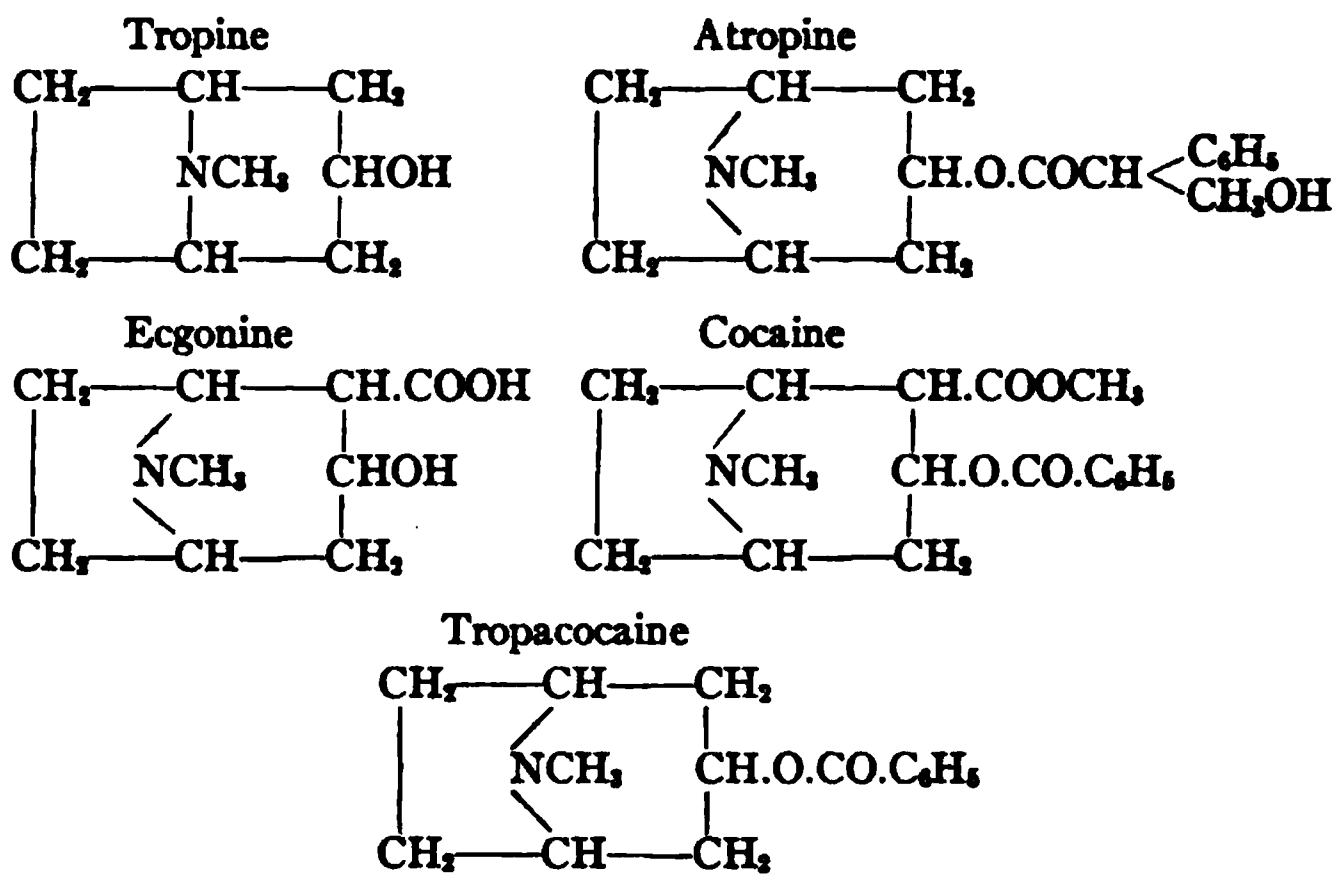
Fluidextract, 0.5 per cent. alkaloid, 30 minims (2 c.c.).

Wine, 6.5 per cent. of fluidextract, with red wine, etc., 4 drams (15 c.c.), this dose containing not less than $\frac{1}{12}$ grain cocaine.

Cocaine chloride (hydrochloride) is the alkaloidal salt employed; dose, ½ grain (0.03 gm.). The 5 per cent. *oleate of cocaine* is official.

Cocaine chloride, $C_{17}H_{21}NO_4.HCl$, is soluble in 0.4 part of water and 2.6 parts of alcohol, and is insoluble in the oils. (For oily solution, the pure alkaloid must be employed.) It is decomposed at a temperature of about 98° C., so its aqueous solution cannot be sterilized by boiling. Its solutions are not antiseptic, and frequently show a growth of mold. This mold development may be retarded by the addition of boric acid. The following

formulæ show the close relation between atropine, cocaine, and tropacocaine.



Pharmacology.—Coca leaves and their preparations are employed only to a very limited extent, and chiefly in the form of coca wine; but cocaine is of great importance pharmacologically, for it is very extensively employed as a local anesthetic, has marked poisonous properties, and is one of the vicious "habit-drugs."

Local.—Cocaine is a general protoplasmic poison, capable of irritating and destroying cells, or of stopping the motions of leukocytes, amebæ, and ciliated cells. Solutions about 5 per cent. in strength injected hypodermatically may result in death of tissue, which shows either as a necrotic area of the skin or as a sterile abscess; the application to the eye may, for the same reason, result in cloudiness or ulceration of the cornea. This effect is not usually seen, but it occurs often enough to be of importance.

From application to mucous membranes or injection beneath the skin there promptly follows complete abolition of pain, from depression of the ends of the sensory nerves or their adjacent nerve-fibrils. In addition, there is local constriction of the arterioles from stimulation of both muscle and vasoconstrictor nerve-endings. The constriction of the vessels is not so great as that from adrenaline. The anesthesia and constriction come on in one to four minutes and last from fifteen minutes to one hour.

The drug cannot penetrate the unbroken skin. The author kept a finger for fifteen minutes in a 20 per cent. aqueous solution

of cocaine chloride, and it showed neither anesthesia nor blanching, though one drop of the liquid on the tongue was quickly followed by loss of sensation. But cocaine is readily absorbed through mucous membranes or the moist parts of the vulva. After the injection or application there may be a momentary irritation, but very quickly there is complete loss of the sense of pain, with shrinkage and paling of the part from comparative bloodlessness. Any mucous membrane to which the drug can be directly applied becomes shrunken and anesthetic in this way, *e. g.*, membranes of the nose, throat, mouth, esophagus, stomach, rectum, vagina, urethra, bladder, and conjunctiva. In the hypodermatic use the drug is injected just beneath the epidermis, and its action is prolonged and intensified by the addition of adrenaline. This further constricts the vessels and prevents the too ready removal of the cocaine by the circulation. For the same reason it tends to make the skin incision bloodless. In a finger or toe the same effect may result from the application of a tourniquet or band to impede the venous return flow.

In the anesthesia, though the sense of pain is promptly lost, the sense of touch is not so readily abolished, and the temperature is scarcely affected, if at all; hence the touch of an instrument or the heat of a cautery may be felt, though pain is absent. The drug at first tastes bitter, but the taste for bitter soon becomes completely abolished, while that for sweet and sour merely becomes dulled, and taste for salt is not affected. If applied in the nose, the sense of smell is abolished.

It has been found that anesthesia is produced if the drug is applied to any part of the nerve, from the nerve-ending to the posterior root; so anesthesia in therapeutics may be obtained—(*a*) by the application of the solution to a mucous membrane; (*b*) by its injection beneath the mucous membrane or skin; (*c*) by its injection into the nerve; or (*d*) by its injection into the spinal canal, so that it may reach the posterior roots. This last method is known as "spinal analgesia" or "spinal anesthesia." Cocaine has not the marked selective action of atropine, but from 10 c.c. of 1 to 3 per cent. solution Ritter (1909) obtained in dogs a general anesthesia lasting from fifteen to thirty minutes. The dogs were fully awake, but quiet and indifferent and insensitive to pain.

The drug affects sensory nerves very readily, but not so readily the motor nerves. If both sciatics of a frog be exposed high up in the thigh, and a little cocaine injected into the substance of one of them, an electric stimulus to the nerve on the uncocainized side (or above the cocainized area on the other side) produces the usual reflex results, notably contraction of the splanchnic

no feeling of hunger so long as food is kept out of their sight, but the appetite returns if they see or smell appetizing food. Probably there is diminished sensation in the stomach and in the mouth, and consequent absence of the effect on appetite of reflexes from these regions, while the psychic elements in the production of appetite (the sight or smell of food) remain intact. The psychic stimulation is also probably a factor in producing increased power to work. It is said that 100,000 000 pounds of the leaves are used annually in South America, the people chewing them with the addition of a little chalk or lime.

These effects have not been obtained in other localities, and consequently have been attributed to some unexplained property which is confined to the fresh or freshly dried coca leaves. But Sollmann thinks that these effects have failed in northern regions because the drug has not been tried in conditions of marked hunger and fatigue.

Disagreeable central effects upon the alimentary tract which not infrequently follow the absorption of cocaine, as in spinal anesthesia, are nausea, vomiting, and diarrhea. The cause of these is not known.

Systemic Effects.—The systemic effects are not made use of in therapeutics, and may be studied rather because of their manifestation in poisoning.

Heart.—In perfusing the isolated heart the addition of cocaine does not change the rate or force of the beat, therefore neither the muscle nor the accelerator endings nor the vagus endings are affected. But in the intact mammal, after a moment of slowing from slight vagus center stimulation, the heart beats faster, and as it does not do so when both accelerators are cut, the effect must be stimulation of the accelerator center. The vagus endings retain their sensitiveness, for even late in the poisoning stimulation of a vagus nerve results in slowing.

After lethal doses the heart eventually becomes weak and slow from direct muscular depression (or perhaps vagus stimulation), and death may take place from cardiac failure. Occasionally, an unexplained, almost instant, collapse follows the absorption of the drug, even when it is used locally. In the hearts of cold-blooded animals, C. C. Lieb has repeatedly obtained auriculo-ventricular dissociation (heart-block).

Arteries.—The vasoconstrictor center is stimulated, and blood-pressure rises; in severe poisoning this center is depressed. From ordinary amounts there is no direct effect upon the arteries, such as occurs from the local application, as the drug is not sufficiently selective in its great dilution by the blood.

Crile calls attention to the important fact that after an in-

travenous injection of cocaine the splanchnic arteries are more resistant to influences which usually cause their dilatation, *e. g.*, shock, handling the viscera, etc.

Respiration.—The respiratory center is strongly stimulated, and the respiration is increased both in rate and in depth. Death is usually due to respiratory failure, though it is not so always.

Cerebrum.—This is stimulated in much the same way as with atropine, even the local use of the drug being followed by talkativeness and cheerfulness, and even delirium and cerebral convulsions. But as an intellectual stimulant it seems to rank higher than atropine, for the cocaine jag is characterized by increased intellectual power and self-possession, in addition to loquacity. The reaction time is shortened, and it is more difficult to put and keep an animal under chloroform or ether, *i. e.*, cocaine antagonizes narcosis.

The *motor areas* of the brain are stimulated, and also *the reflex centers of brain and cord*, and there is a tendency to motor activity and restlessness, so that the patient wants to walk about. A dog will run amuck, usually in a circle, and quite indifferent to his surroundings.

The ergograph shows an actual increase in muscular power. All these things are evidences of true central stimulation, exactly the opposite of the effect of alcohol or morphine.

After highly poisonous doses the stimulation is followed by depression, stupor, cerebral (not spinal) convulsions, and coma.

Medulla.—The respiratory, vasoconstrictor, and accelerator centers are stimulated. Whether the vagus center is stimulated to any great extent or not is a moot question. In poisoning, the thermogenetic center in the caudate nucleus is affected, so that the temperature may rise several degrees.

Muscle.—There is no direct effect, but the motor areas are stimulated, so that muscular power is increased and fatigue is lessened.

Temperature.—See under Medullary Centers. The rise in temperature has probably the same explanation as that after atropine. The temperature does not rise in chloralized animals.

Excretion.—All, or nearly all, is destroyed in the body, so there are no remote local effects in the urinary passages, as in the case of atropine. The urine is sometimes increased, sometimes diminished, probably through changes in the kidney circulation. The effect upon it is unimportant.

Untoward Effects.—Untoward effects following its use for anesthesia are:

(*a*) *From protoplasmic irritation*—cloudiness or ulceration of the cornea; necrotic area or sterile abscess at the site of injection.

Anesthesin, the ethyl ester of para-amido-benzoic acid, has the same uses and dosage as orthoform. It is slightly soluble in water, and more readily so in alcohol and the oils.

Propæsin, para-amido-benzoic-acid-propyl ester is a crystalline powder, slightly soluble in water and moderately so in alcohol. It is used in the same way as the last named, in doses of 5 grains (0.3 gm.) or in 10 per cent. ointment. *Dipropæsin* is a combination of one molecule of urea with two of propæsin. It is anesthetic in an alkaline medium.

Chloretone, chlorbutanol, is sometimes employed in the same way (see under Hypnotics), in powder, tablets, spray, etc., as a local anesthetic.

Holocaine, para-diethoxy-ethenyl-diphenyl-amidin chloride, is very soluble in water, but more irritant and more toxic than cocaine. In forty-five seconds a 1 per cent. solution produces an anesthesia of the eye which lasts ten or fifteen minutes, without any effect on pupil, accommodation, intra-ocular tension, or the arterioles.

Dionine, di-ethyl morphine chloride, is soluble in 7 parts of water, and is used in 5 per cent. solution to dilate the pupil, to lessen intra-ocular tension, and to abolish pain in the eye. Snyder prefers it to eserine in glaucoma. At first it causes great irritation and even chemosis, but this soon disappears. Its systemic effect is similar to that of codeine. (See Morphine.)

Yohimbine is an alkaloid yielded by a tree of the *Apocynaceæ* of German West Africa. Its solutions decompose on boiling and deteriorate on keeping. It is less anesthetic than cocaine and dilates the pupil, but it so strongly dilates the vessels that to prevent hyperemia a 2 per cent. solution requires to be mixed with an equal quantity of epinephrine solution.

Taken by mouth, yohimbine is said to cause a dilatation of the cutaneous vessels, to stimulate the lower part of the spinal cord, to increase sexuality, and to induce erections of the penis which may or may not be accompanied by sexual desire. Dose, ⅛ grain (0,008 gm.), or in 2 per cent. solution hypodermatically 8 minims (0.5 c.c.). A number of veterinary writers have reported aphrodisiac effects in cows, pigs, and horses.

Schleich's infiltration anesthesia was famous at one time. He used solutions of the chlorides of morphine and cocaine in three different strengths in 0.2 per cent. solution of sodium chloride. The strongest of his solutions contained 0.2 per cent. of cocaine and 0.025 per cent. of morphine.

Other local anesthetics are the *ethyl chloride* spray, which freezes the part, and is only momentary in its effects, and *phenol,*

the action of physostigmine, and *calabarine* that of strychnine. Physostigmine in solution is decomposed by light or heat, and a reddish color indicates diminished activity.

Preparations and Doses.—

Physostigma, 0.1 per cent. of alkaloid; dose, 1½ grains (0.1 gm.).

Extract, 2 per cent. of alkaloid; dose, ⅛ grain (0.008 gm.).

Tincture, 10 per cent., 15 minims (1 c.c.).

Physostigmine salicylate, soluble in 72 of water and 13 of alcohol, and *physostigmine sulphate*, deliquescent and freely soluble in both water and alcohol, are given in doses of $\frac{1}{60}$–$\frac{1}{30}$ grain (0.001–0.002 gm.).

Pharmacologic Action.—Physostigmine stimulates the secretory nerve-endings of glands and the nerve-endings of striated and smooth muscle. It therefore antagonizes the effects of atropine upon secretion, upon the action of smooth muscle, and upon the eye; and antagonizes curare in its effects upon striated muscle. It has no effect on sensory nerve-endings.

Secretion.—Physostigmine is not employed in medicine to increase secretions, for by arteriole constriction and the cutting-off of the blood-supply of the glands the amount of the secretion is limited.

Muscle.—Its effect upon the action of smooth muscle is strongest in the alimentary tract, so that it may be employed, either by mouth or hypodermatically, as a cathartic. It also tends to cause contraction of the bladder, ureters, bronchi, and spleen, and perhaps also of the uterus.

Its effect upon the action of striated muscle is shown in the isolated gastrocnemius by increased irritability and increased power to lift a load. Irregular stimulation in man is also indicated by peculiar fascicular spasms or twitchings of the muscle, as in the temporal or orbital muscles when the drug is used in the eye, or in the muscles of the limbs in poisoning. It is directly antidotal to the peripheral action of curare, and presumably acts upon the same structures.

The Pupil.—If a drop of 1:200 aqueous solution of eserine is placed in the eye, contraction of the pupil begins in one or two minutes and reaches its maximum in one-half to one hour. The marked contraction lasts from twelve to thirty-six hours, and the normal size of the pupil is regained in from two to four days. The contraction is due to stimulation of the ends of the third nerves, physostigmine not contracting the pupil after degeneration of the nerve (Anderson).

Accommodation.—Through similar action on the ends of the

[illegible] the skin covered with sweat, there are vomiting, diarrhea, [illegible] in the abdomen. The loss of muscular power begins in [illegible] and ascends, and is accompanied by twitching or tremor. [illegible] at first slow and the arterial pressure good; later the [illegible] weak and slow, and the blood-pressure is lowered. [illegible] is at first rapid and deep, then becomes shallow [illegible] perhaps asthmatic. Death occurs from paralysis [illegible] The *antidote* is atropine for the asthma, the [illegible] intestinal cramps; if necessary, the patient [illegible] for collapse, bearing in mind that the heart itself [illegible] Sepp and Meltzer recommend magnesium sul- [illegible] antidotal. It can be used subcutaneously or in [illegible] the dose being 1 dram (4 c.c.) of a 25 per cent.

[illegible] The extract in pills, and the salts of physostig- [illegible] are used as cathartics. Since not many [illegible] cathartics when administered hypodermatically, [illegible] power of physostigmine may be of value in [illegible] or postoperative conditions.

[illegible] salts, usually in a solution of 1 : 200, [illegible] in the eye to lessen the high intra-ocular [illegible] and, after drugs of the atropine class, [illegible] of the pupil and accommodation to normal. [illegible] to pilocarpine because their action lasts [illegible] complete, and there is no noteworthy pre- [illegible] intra-ocular tension.

[illegible] is the nervous spasm of the eyelid and tem- [illegible] may occur frequently during several hours.

PILOCARPUS (JABORANDI)

[illegible] *Pilocarpus jaborandi* or of *Pilocarpus micro-* [illegible]), yielding, when assayed, not less than [illegible] alkaloids. It is a Brazilian shrub.

[illegible] The alkaloid *pilocarpine*, also isopilocarpine [illegible] with similar action, and jaborine, which acts [illegible] occurs in too minute quantity to have any

[illegible] **and Doses.**—

[illegible] 0.5 per cent. alkaloid; dose, 30 grains (2 gm.).

[illegible] 0.4 per cent. alkaloid; dose, 30 minims (2 c.c.).

[illegible] *chloride* and *pilocarpine nitrate;* dose, 1/6 grain [illegible] gm.), the former being readily soluble in alcohol [illegible] water, the latter in water but less readily in [illegible] (1 : 60).

Elimination.—In the sweat, urine, and saliva.

Toxicology.—As in physostigmine poisoning, there is prostration without loss of consciousness. There is at first excessive vagus action and depression of the vasoconstrictor center, with slowed or intermittent heart-beat (vagus standstill or vagus heart-block) and low blood-pressure. Later there is slow, feeble heart-beat and collapse.

The pupil is strongly contracted, the skin flushed and profusely sweating, and the saliva abundant. There may be nausea, vomiting, diarrhea, and abdominal cramps. The respiration may be labored, asthmatic, with the physical signs of increased bronchial mucus or edema over both lungs; there may be muscular relaxation, beginning in the lower limbs and ascending. Consciousness, though dulled, persists until near the end. Death takes place in collapse, with edema of the lungs.

The *treatment* is atropine hypodermatically, and the general treatment for collapse, especially artificial respiration. The atropine serves to overcome the asthmatic breathing, to lessen bronchial secretion, to diminish cramps in the abdomen, and to check excessive vagus action.

Therapeutics.—The fluidextract is added to *hair-washes*, the pilocarpine salts being, as a rule, considered too expensive.

In the *eye*, a 1:200 solution of pilocarpine chloride is used in glaucoma, and to hasten contraction of the pupil after mydriatics; but physostigmine is usually preferred.

Internally, it has been employed in chronic congestive conditions of the middle ear, in labyrinthine affections, and in congestive conditions of the eye. Its good effects seem to depend largely on the resulting diaphoresis. It has also been used as an expectorant in the dry stage of bronchitis, but it makes profuse sweating and salivation.

Its chief use is as a *diaphoretic* in nephritis with uremia and in dropsy. Tyson recommends 10 minims of the fluidextract three times a day, or a daily dose of ¼ grain of pilocarpine chloride. Because of its tendency to depress the heart or produce edema of the lungs, its effects must be watched; and it should not be employed if the heart is weak.

MUSCARINE AND MUSHROOM POISONING

Muscarine is an alkaloid contained in the mushroom known as the fly agaric, *Amanita muscaria*, and in some other agarics. Its actions are very similar to those of pilocarpine, but stronger, hence in poisoning by the fly agaric we get the same symptoms as from pilocarpine poisoning. The symptoms come on very quickly. *Muscarine is not destroyed by cooking.* Atropine is the

Fat.—In a sense there is a protective garment about a fat person, the thick, poorly conducting layer of fat interfering with heat-loss; so that if the internal temperature is raised, an excessive amount of sweat is poured out in the vain effort of the body to cool itself. On a hot, humid day a fat man sweats more profusely, yet suffers more from the heat than the thin man. If a fat person ingests no water while carrying out diaphoretic measures, the body tends to form water from the fat, and so lessen its adipose deposit. Von Noorden says that 100 grams of fat yield 107 grams of water, and he states that restriction of the water intake produces a loss of fat. But he quotes Heilner and also Henneberg as authorities for the statements that in experimental animals abundant water-drinking increases fat catabolism, and in stock-raising renders it very difficult to fatten animals. Yet by vigorous daily exercise, wearing heavy sweaters, limitation of the fluids, and regulation of the food ingested, a fat man may lose 40 or 50 pounds of his weight in a few months and yet feel in splendid condition.

The Character of the Sweat in Diaphoresis.—The normal secretion of the sweat-glands is of low specific gravity and of faintly alkaline reaction, and there are various salts present. The slight acidity sometimes noted is due to admixture with the sebaceous secretion. With copious sweating by raising body-heat, or by drugs which do not act specifically on the sebaceous glands, we get a slightly alkaline secretion. With pilocarpine, on the contrary, which specifically stimulates both the sweat and the sebaceous glands, the secretion tends to be acid, or at least not alkaline, owing to the presence of the fatty acids of the sebaceous material.

The Relation of Diaphoresis to Nitrogenous Excretion.—The ordinary insensible perspiration does not contain any appreciable nitrogenous matter (Lusk). The average of many tests by different experimenters gives 0.068 gm. nitrogen per day in skin elimination.

Benedict (1906) got 0.071 gm. nitrogen per day in the whole cutaneous secretions, both sebaceous and sweat, of a resting man. "But when the sweat was increased, as in a man at moderate work, the nitrogen from the skin rose to 0.13 gm. per *hour*, and in a man at hard work to 0.22 gm. per hour. The nitrogen of these larger quantities represented urea, uric acid, creatinin, and other constituents of urine." Therefore, copious sweating from hard work, which Atwater and Benedict found might be eight times the normal sweating, represented the loss of 1 gm. of nitrogenous excreta in five hours. This shows that the sweat-glands of normal persons can, to some degree, be made to take on a function of the kidneys. But in this work there was greatly increased muscular

1.3 gm. of urea from profuse sweating, and this is too little to be of moment to the kidneys. Thus *sweating in nephritis must be considered chiefly of use in removing water and perhaps chlorides rather than urea or other nitrogenous waste.* Therefore, the diaphoresis should be employed to lessen the edematous condition or hydremic plethora, rather than to remove nitrogenous waste.

In intestinal putrefactive toxemia with indicanuria, indol has been detected in the perspiration.

In a simple hot bath, as in the more elaborate baths, sweating may be profuse, and afterward may continue for many hours in excess of normal if the person remains in a warm room or in bed.

Therapeutics and Administration.—1. *To lower temperature,* in mild fevers—the liquor ammonii acetatis, 2 drams, or spiritus ætheris nitrosi, 1 dram. The effect of these is probably almost nothing.

2. *To overcome chill or cold*—by relieving internal congestion and reëstablishing proper cutaneous circulation. Hot lemonade at bedtime, whisky and hot water, Dover's powder, and a hot bath are the favorites, with extra bed-clothes. Dover's powder is in extensive use by both physicians and the laity to produce sweating, especially if there is pain or restlessness. But unless it is given with a copious hot drink and extra bed-clothing is piled on, the chances of its producing *profuse* sweating are very small. It is given in 5- or 10-grain doses, and is often followed the next morning by nausea, headache, and a feeling of lassitude.

3. *To lessen obesity*—exercise with heavy woolen clothing, Turkish baths, hot baths, restriction of liquids ingested.

4. *To assist the kidneys* in the removal of accumulated poisons, as in uremia, and possibly in gout, rheumatoid conditions, eclampsia, and other toxemias. Hot-pack, vapor baths, etc., with or without pilocarpine, and, if there is no edema, with copious drafts of water.

5. *To lessen edema and promote the absorption of dropsical effusions*—hot-pack, vapor baths, etc., with dry diet, very little water being ingested. Sometimes with pilocarpine. It must be understood, of course, that dropsical fluid disappears by way of the lymphatics through improvement in the circulation; edema fluid may be reabsorbed from the tissue-spaces if by sweating the blood loses water.

6. *To lessen congestion of the internal eye* and of the middle and internal ear—especially by pilocarpine.

7. *To hasten the outbreak of the rash* in measles and other exanthemata. Hot baths for this purpose are in common employment.

8. *Local sweating with high temperature is used in chronic rheumatism,* rheumatoid and gonorrheal arthritis, and other joint

We might review very briefly the **functions of the different parts of the kidneys:**

The Glomerulus.—While there seems to be no doubt that this acts largely, if not almost altogether, as a mechanical filter, there is some evidence that its cells may, in addition, select and secrete certain of the elements of the blood. Brodie believes it to be an expulsor organ, capable of expansion and contraction.

The Tubules.—That the tubules have the power to reabsorb water and some of its dissolved substances is apparent from a number of experiments. Cushny showed that not only was water absorbed, but that there was a differential reabsorption of certain of its salts, apparently in proportion to their diffusibility, *e. g.*, sodium chloride more readily than sodium sulphate. He found also that in marked diuresis the proportion of these salts in the urine was more nearly equal; and he figured that reabsorption failed to take place because of the rapidity of the passage of the liquid through the tubules. Moreover, destruction of the tubule cells experimentally or by disease is regularly followed by increase of urine excretion.

That the tubules have also a specific secretory power is suggested by the results of the injection of sodium sulphindigotate into the blood. Within a minute or two the urine secreted is blue, showing that the pigment passes out in the urine. If the kidney is at once removed and the coloring-matter fixed by perfusion with alcohol, microscopic examination shows the tubule cells deeply stained with blue, while the glomeruli are not stained at all. This suggests that the pigment has passed through the tubule cells (presumably was excreted) rather than through those of the glomerular capillaries. Again, if the blood-pressure is reduced below 40 mm. mercury (below which pressure all urine flow ceases), the cortex alone is blue, and the pigment is found deposited in granules in the striated epithelial cells and the lumen of the first and second convoluted tubules. After the injection of uric acid in a solution of piperazin Starling found uric acid in the cells and lumen of the convoluted tubules. Nussbaum's experiment on the reno-portal vein of the frog and some experiments on poisoned kidneys also point to a specific secretory power.

By injecting acid indicators into the blood it may be shown that the glomerular fluid is alkaline, and that the urine becomes acid in the convoluted tubules; if it is hurried through the tubules by active diuresis, it is less acid and may be alkaline.

Without entering further into the theories of kidney action, which are not yet soundly established, and can be read up in any recent book on physiology, we will assume that the *function of the glomerulus* is to pass from the blood to the uriniferous tubules

large quantities of an alkaline fluid which contains urea, chlorides, phosphates, sulphates, and under some circumstances sugar and other substances, in the proportion in which they occur in the blood. And that the *functions of the tubules are:* (1) *To change the reaction* of the glomerular fluid to acid. (2) *To add to it certain substances* by excretion, such as urea, uric acid, creatinin, urinary pigment, phosphates, and, under certain circumstances, water. Hans Meyer says that no known diuretic can increase the excretion of uric acid and phosphates. (3) *To concentrate the urine*, by the reabsorption of much of its water and of some of its dissolved substances. These are reabsorbed somewhat according to their absorption power, *i. e.*, sodium chloride readily, sulphates less readily, and urea not at all. But physiologic conditions predominate over physical, for foreign substances, though readily diffusible, such as potassium iodide, or even sodium chloride when this is in excess, will be passed out without apparent reabsorption.

The urine is, therefore, made up essentially of—(1) water, (2) such dissolved substances as have been removed from the blood in the glomeruli and have escaped reabsorption, and (3) the substances excreted by the tubule cells. Either its *quantity* or its *quality* may be changed by an alteration—(1) in the constituents of the blood; (2) in the filtration or secretory power of the glomeruli; (3) in the secretory power of the tubules; or (4) in the reabsorptive power of the tubules; but in the production of diuresis we are not always certain which of these are the factors involved.

On account of these complex factors we must not forget, in treating patients, that the volume of the urine is made up of water, and that, therefore, *the quantity of urine excretion is not necessarily a measure of the excrementitious materials* that are being removed from the body. Indeed, von Noorden states that a concentrated urine may carry out just as much deleterious matter as one less concentrated. As the normal powers of healthy kidneys are vastly more than sufficient to maintain a proper blood composition, our endeavor in disease must be to restore the kidney functions or to minimize the amount of kidney activity required. We cannot confer upon the kidneys any abnormal powers, or functions new to kidney tissue.

From these remarks it will be seen that the site of the diuresis may be the glomerulus or the tubule, or both; and that *diuresis may be brought about by:*

I. *Measures which increase the glomerular fluid.*
   (*a*) By increasing the blood-flow through the kidney.
   (*b*) By lowering the osmotic pressure of the blood.
II. *Measures which increase the tubular secretion.*
III. *Measures which decrease the tubular reabsorption.*

than normal, the tissues or tissue-spaces having been drawn upon for a diluting fluid. If an isotonic or hypotonic saline solution is injected into a vein, swallowed, or administered by rectum, this hydremic plethora results without the imbibition of fluid from the tissues or tissue-spaces. In dropsy, hydremic plethora results from the absorption of the dropsical fluid.

In hydremic plethora, under the influence of the slightly raised arterial pressure and the lessened viscosity of the blood, this swollen volume of blood tends to promote rapid blood-flow, and, as a consequence, to favor transudation of the excess of fluid through capillaries. The kidney capillaries are the ones by which the body gets rid of excessive fluid; therefore if the kidneys are functionating properly, there is diuresis, and the excess of water with certain dissolved materials is rapidly got rid of. Hydremic plethora and its resulting diuresis may be the consequence of the absorption of dropsical fluid, as under the administration of digitalis.

It may be produced intentionally by the ingestion of water, or of solutions of dialyzable substances, so that these are diuretic.

Of dialyzable substances, those with a pronounced diuretic action are:

(*a*) *Inorganic Salts.*—Sodium sulphate, sodium chloride, sodium or potassium bicarbonate, magnesium salts. Except the bicarbonates, these are not employed as diuretics.

(*b*) *Organic Salts.*—The acetates, citrates, and tartrates, which break down into carbonates in the blood. They are potassium acetate, potassium citrate, potassium bitartrate, potassium and sodium tartrate, magnesium citrate, liquor ammonii acetatis, liquor ferri et ammonii acetatis (Basham's mixture). The best of these is potassium acetate.

(*c*) *Urea, Dextrose.*

All these substances tend to have an effect upon the urination in direct proportion to the osmotic pressure which they exert. In hydremic plethora, if the kidneys are not functionating well, as in chronic nephritis, the excess of water tends to transude through the systemic capillaries and to favor the production of edema and dropsy.

Water.—Ordinary drinking-water is hypotonic, and is practically unabsorbed by the stomach. But it imbibes salts from the food or mucus, or from the superficial cells of the alimentary tract, or takes up the sodium chloride which is formed in the duodenum by the neutralization of the hydrochloric acid of the gastric juice. Hence it becomes a salt solution, and, instead of passing on through the intestine to the rectum, is absorbed. Therefore when water is ingested it does not normally pass out with the feces; and under ordinary conditions of absorption, no matter how much is

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.....	153 "

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:es place through the tubules, or by impair-
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.ı. Magnus says that for each salt (substance)
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·ss with an increased secretion of water. It may be
·is the level of this "secretion threshold" is lowered.
·ut abundant supply of water there is no diuresis.

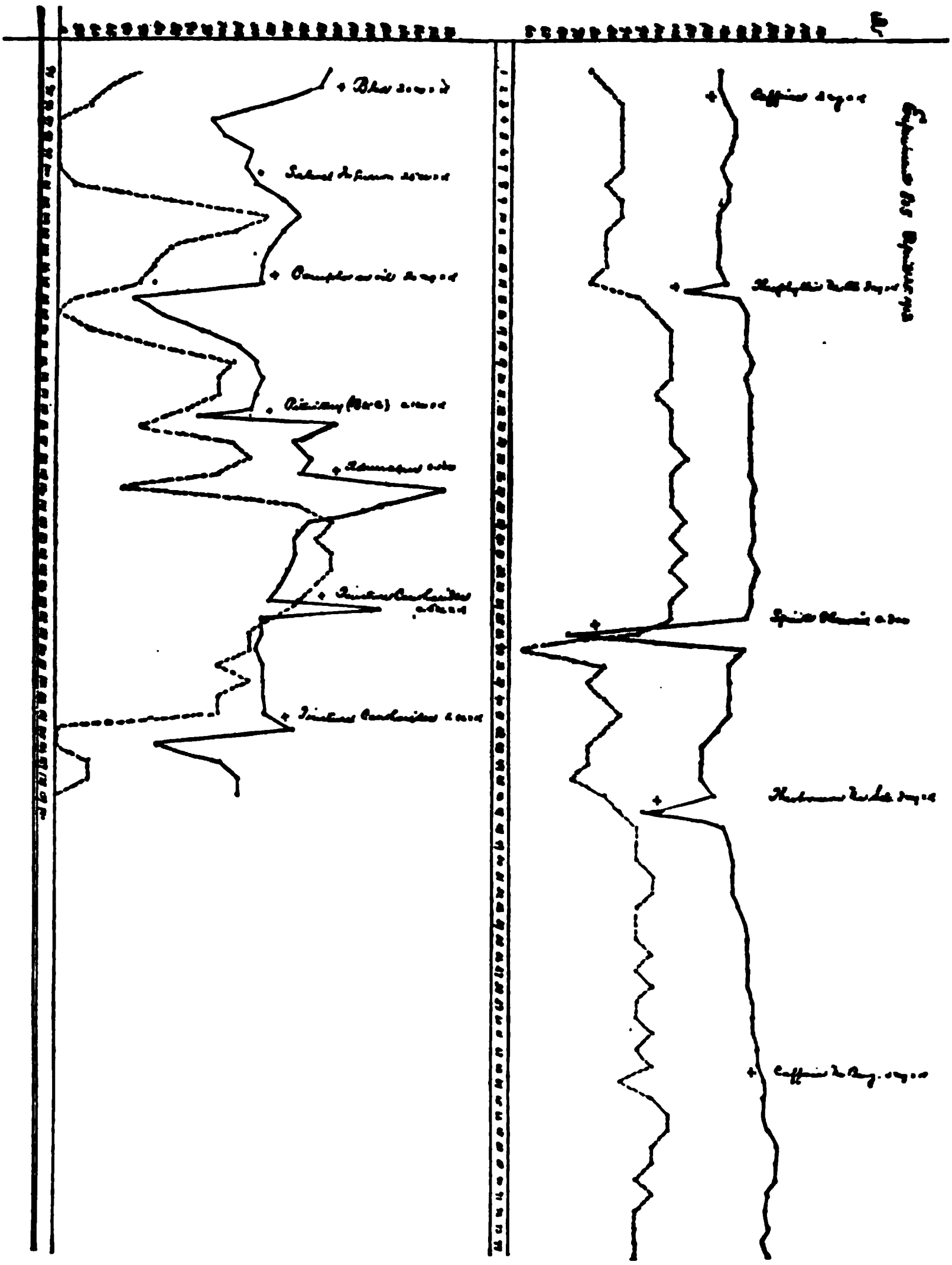

Fig. 52.—Drawing made to scale from tracings taken from a dog by C. C. Lieb. Horizontal line of figures, time in minutes. Black line, arterial pressure; dotted line, urine flow. The close relation between general blood-pressure and urine flow is striking. The drugs, in the order used, with dose per kilo, are: *Caffeine*, 2 mg., urine little affected. *Theophylline acet-sodium*, 3 mg., urine much increased. *Spirit of nitroglycerin*, 0.3 c.c., urine decreased. *Theobromine sodium salicylate*, 3 mg., urine increased. *Caffeine and sodium benzoate*, 4 mg., continues theobromine effect. *Animal bled*, 20 c.c. per kilo, great fall in urine. *Saline infusion*, 25 c.c. per kilo, great increase. *Camphor in oil*, 20 mg., decided fall. *Pituitary extract*, 0.1 c.c., fall followed by rise. *Adrenaline solution*, 0.1 c.c., fall followed by rise. *Tincture of cantharides* was then given in amounts large enough to produce inflammation of the kidney.

diuretics. In either case, after a few days' exposure to the poison, the lesions tend to extend and become combined; but when the poison is stopped, the kidneys heal and do not show the lesions of chronic nephritis (Pearce).

When the human kidneys are impaired, as in nephritis, there may be abnormal retention of various substances, *i. e.*, the kidney loses its power to excrete to the full degree. According to von Noorden, in *acute nephritis* the following substances continue to be well excreted, viz., uric acid, the xanthine bases, aromatic bodies, ammonia, amido-acids, chlorides, and carbonates; while among those which are excreted with difficulty and tend to be retained are urea, creatinin, urinary pigment, hippuric acid, phosphates, inorganic sulphates, and in some cases water.

In *chronic nephritis* with edema we have little information to guide us in our choice of diuretics, and our best plan is to use a saline diuretic with one of the caffeine series, such as diuretin. Pearce has shown that kidney injury alone is insufficient to cause edema. There must be, in addition, general capillary permeability and hydremic plethora.

(*c*) *Tissue retention* of water as a cause of edema is a subject not fully understood. In chronic edematous states it is customary to put the patient on a diet very low in sodium chloride, the so called "salt-free" or "salt-poor" diet. This reduces the sodium chloride in the urine, but seems to make little alteration in the percentage of sodium chloride in the blood-plasma. It is, however, an effective measure in many cases.

(*d*) *Abnormal permeability of the capillaries of the body* is undoubtedly the result of poisons, as in arsenic poisoning and uremia.

It is to be remembered that diuresis requires water as its medium, so that to promote the elimination of poisons, copious drafts of water should be administered with the diuretic. If, however, there is edema or any degree of water retention, all fluids should be restricted.

ANTIPYRETICS

Antipyretics are remedies which tend to reduce the temperature in fever. Many remedies which have this property are considered elsewhere, because the antipyretic property is not the dominant one; for example, whisky and digitalis. The reduction of temperature may be brought about by cold or by drugs.

Cold.—Some of the methods for applying cold are: The cold bath, the cold-pack and the drip sheet; and for local use the cold compress, the ice-water coil or ice-bag, the rectal irrigation with ice-water, the cold spinal douche, etc.

The cold bath is employed in typhoid fever. In the *tub-bath*

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... zol, and has a slightly bitter
... the alkaloids, and is pre-
... and some other alkaloidal
... poisonous compound. With
... it gives a deep-green color
... salts a deep red; with chloral
... salicylate it liquefies; with
... alkaloids it forms soluble
... gm.). For local application it
... aqueous solution. Close relatives
... phenyl-dimethyl pyrazolon, and

... en-acetamide, $C_6H_5.NH.CH_3CO$.
... soluble in 180 parts of water and
... water is increased by acids and
... grains (0.25 gm.).

... *mpound acetanilid powder* (pulvis
... contains acetanilid, 7 parts, caf-
... bonate, 2 parts. Close relatives
... yl-acetanilid, and *salophen*, ace-

... $C_6H_5.NH.CH_3CO$, more familiarly
... ame phenacetin, is a derivative of
... of water and 12 of alcohol, and
... formula shows that phenacetin
... -acetanilid, but it is not a direct
... may better be placed in a separate
... mpounds. It is not readily soluble
... gm.). The other phenetidin com-
... *phenin*, a lactic-acid derivative;
... ivative; and *apolysin* and *citrophen*,
... tric acids.

... These drugs all reduce temperature
... gesic, are all nerve sedatives, and are
... action is mild, but is the same in
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... lly, and phenacetin is bland.

is freely soluble in water and alc[illegible]ion were in
taste. It is a body closely resemb[illegible] fever results
cipitated by tannic acid, alkalies [illegible] make the heat-
reagents. With calomel it forms a [illegible]hether or not the
spirit of nitrous ether or other nitri[illegible] is still a question.
(iso-nitroso-antipyrine); with ferri[illegible] surface cooling from
hydrate, naphthol, phenol, and sod[illegible] the skin being the site
caffeine, quinine, and some oth[illegible] temperature changes are
double salts. Dose, 4 grains (0.2 [illegible] heat-producing response of
is employed in 5 to 25 per cent. a[illegible]ce rather than to general
are *pyramidon*, dimethyl-amidop[illegible]nt fever results from this
salipyrine, antipyrine salicylate. [illegible] when the skin vessels are still

Acetanilidum, acetanilid, phe[illegible] *i.e.*, when heat-loss is at a
has a slightly biting taste, and i[illegible]
in 2.5 of alcohol. Its solubility [illegible]ers which have been studied in
decreased by alkalies. Dose, 4 [illegible]ase in the nitrogen elimination

An official preparation is [illegible] increase in the amount of fats
acetanilidi compositus), whic[illegible] shown by the elimination of CO_2;
feine, 1 part, and sodium bi[illegible] not greatly increased. Just the
of acetanilid are *exalgine*, n[illegible] active exercise, in which there is
tanilid-salicylic acid. [illegible]ion of CO_2 and only a moderate

Acet-phenetidin, $C_6H_4.C$[illegible] urine.
known under the proprieta[illegible] this heat-regulating center to the
phenol. It is soluble in 9[illegible] The heat-regulator is set at a certain
is almost tasteless. The [illegible] warmer, the mercury rises or a
might properly be called [illegible] by making an electric connection
derivative of acetanilid. [illegible] dampers in the furnace so that the fire
group with other pheneti[illegible] down the registers so that the room
in water. Dose, 8 grain[illegible] temperature of the room falls below that
pounds worthy of note [illegible] the dampers or registers are opened
malakin, a salicylic-acid [illegible] into the room. Now, to carry out the
the mono- and tri-phen[illegible] center in the human body may be

Pharmacologic Acti[illegible] normally set for a temperature between 98°
in the same way, are a[illegible] temperature goes up a degree or two, the center
all antiseptic. Their [illegible] result either in a lessening of heat-pro-
kind as that of the ph[illegible] in muscular and circulatory activity,
closely related chemic[illegible] *i. e.*, by dilatation of the cutaneous
as exhibited in the [illegible] the contrary, if the temperature falls
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Locally, antipy[illegible] vessels and the stoppage of sweating.
per cent. solution a[illegible] center has little discriminating
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brane and the ch[illegible] and at the same time to increase the
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THE ANTI-MALARIAL ANTIPYRETICS

CINCHONA

There are two medicinal varieties of cinchona, one the bark of several species of calisaya, and known officially as *Cinchona*, the other the bark of the red cinchona, known as "Peruvian bark," and with the official title, *Cinchona rubra*. These are natives of South America, but many species are cultivated in various tropical countries.

Constituents.—There are about 19 alkaloids, the important ones being *quinine*, *cinchonine*, *quinidine*, and *cinchonidine*. In addition there are quinic, quinovic, and tannic acids. Red bark contains more tannic acid and less quinine than calisaya, but both are required to contain 5 per cent. of total alkaloid. The United States Pharmacopœia specifies that calisaya shall contain not less than 4 per cent. of ether-soluble alkaloid, *i. e.*, quinine, cinchonine, and cinchonidine.

Preparations and Doses.—*Fluidextract* (calisaya); dose, 15 minims (1 c.c.). *Tincture*, 20 per cent. (calisaya); dose, 30 minims (2 c.c.). *Compound tincture* (tinctura cinchonæ composita), 10 per cent. red bark with serpentaria and bitter orange peel; dose, 1 dram (4 c.c.).

The alkaloidal salts, dose, 5 grains (0.3 gm.), are:

Quinine sulphate, $(C_{20}H_{24}N_2O_2)_2.H_2SO_4$, soluble in 720 parts of water and 86 of alcohol. It is readily soluble in dilute hydrochloric, sulphuric, or phosphoric acids, as it forms the soluble double salts, or in the case of sulphuric acid, the soluble bisulphate. *Quinine bisulphate*, $C_{20}H_{24}N_2O_2.H_2SO_4$, soluble in 8.5 parts of water and 18 of alcohol. *Quinine bromide*, soluble in 40 parts of water and 0.67 of alcohol. *Quinine chloride*, soluble in 18 parts of water and 0.6 of alcohol. *Quinine salicylate*, soluble in 77 parts of water and 11 of alcohol. *Cinchonine sulphate*, soluble in 58 parts of water and 72 of alcohol.

A much used preparation is the double *chloride of quinine and urea*, better known as the bimuriate of quinine and urea. It is soluble in its own weight of water, and is, therefore, suitable for hypodermatic administration. It is, moreover, non-irritating. Its solutions are unstable.

Euquinine, not official, is the ethyl carbonic ester. It is insoluble in water and not bitter. Its dose is twice that of the official quinine salts.

Tinctura antiperiodica, N. F. (Warburg's tincture), is a bitter, aromatic, laxative, sedative and antimalarial "shot-gun" prescription. It is made of quinine sulphate, aloes, rhubarb, angelica seed, elecampane, saffron, fennel, prepared chalk, gentian,

changed to a decrease. In a dog an intravenous dose markedly contracted the spleen and caused a decided decrease in the white cells, especially of the polynuclears. He thought the primary rise in man might be due to squeezing out the splenic leukocytes by its contraction. These are notably of the lymphocyte type.

Locally, the inorganic salts are distinctly irritant to raw surfaces and mucous membranes, as when its solutions are used in the rectum or hypodermatically. After a hypodermatic of the chloride of quinine and urea there soon ensues a pronounced local anesthesia which lasts for some hours. Quinine is said to stimulate the growth of hair, and is an ingredient of rum and quinine, eau de quinine, and other mixtures which are sold as hair-stimulants.

Alimentary Tract.—It is intensely bitter, and, given before meals, acts as a bitter to promote appetite. Large doses irritate the stomach and may cause nausea and even vomiting. There is slight retardation in the activity of pepsin and trypsin, while the other digestive ferments are probably not affected. It is to be borne in mind that quinine sulphate, the alkaloidal salt almost universally employed, requires an acid medium for its solution; therefore it is administered after meals.

Quinine is said to retard the absorption of salts, and also probably of other substances (foods and medicines), from the stomach (Sollmann).

Absorption.—If the quinine salt goes into solution it is rapidly absorbed from the stomach and may appear in the urine in fifteen minutes. If the stomach is not acid, the quinine may not dissolve.

Circulation.—In ordinary therapeutic doses there is probably a slight increase in the rate of the heart and a tendency to a rise in the blood-pressure from mild stimulation of the heart muscle and of the arterial muscles. The arterial action is a peripheral one, for on perfusing an isolated viscus, there is contraction of the arterioles, followed in a short time by their dilatation. In large doses there is direct depression of the muscles of the heart and of the arteries, with slow pulse (which occurs after atropine, so is due to muscular depression), and a fall in blood-pressure. From ordinary therapeutic doses the effect on the circulation is negligible.

The *blood* we have already spoken of. Its coagulability is decreased and its white cells are lessened in number and probably also in activity. In bleeding experiments on dogs, de Sandro (1911) noted that dogs given quinine recovered their hemoglobin and red cells less readily than those without quinine.

Cerebrum.—It has the same tendency as the other antipy-

[illegible] is excreted in a few hours. Traces [illegible] or more. From 30 to 90 per cent. [illegible] the urine unchanged, and some is [illegible]. A small amount appears in other [illegible] that traces appear in the milk. [illegible] changes of the skin there may [illegible] a scarlatiniform rash, eczema, urti- [illegible] ing. So frequent are skin rashes [illegible] unusual type regularly elicits the [illegible] you taken quinine?"

[illegible] quinine irritate the kidneys and [illegible] emoglobinuria or hematuria.

[illegible] ctions seem to be favored, and the [illegible] increase the force of the contraction [illegible] causes a tetanic contraction as do [illegible] simply to strengthen the usual [illegible] ctions which take place at this time. [illegible] quinine may produce abortion in a [illegible] seen several cases where abortion in [illegible], though it may not have been [illegible] for malaria. There are also many [illegible] ortion has not followed its use.

[illegible] very small doses, even doses small [illegible] At first there is a slight increase [illegible] the urine, probably due to increased [illegible] there is a marked decrease, and [illegible] the urea and uric acid. The same [illegible] may be absorbed, but less is consumed [illegible] ing-up of proteins. Quinine has, [illegible] to fever, which is associated with [illegible]. There is no evidence of incomplete [illegible] products.

[illegible] oxidation processes are changed [illegible] taken in, and the CO_2 given off, being [illegible] usually taken as a criterion of the [illegible] there is less heat generated by [illegible] to its lessening the destruction of [illegible] temperature in fever almost entirely [illegible] heat; and as it lowers temperature [illegible] cord, it does not exert this action [illegible] center.

[illegible] acts best at about the time of a usual [illegible] and has but little effect in health. It [illegible] temperature as acetanilid, and in [illegible] opsoid, has very little effect. As an

Alimentary Tract.—Its sole value is as a bitter, and for this the preferred preparation is the compound tincture of cinchona. It is not a true tonic, for it tends to inhibit the proteolytic enzymes, to irritate the stomach, and to retard absorption, and does not have any good effect on muscle at all.

Systemically.—It is employed as an antipyretic and analgesic to reduce the pains of *influenza* and the discomfort of a cold. In *neuralgia* and *headache* it is analgesic, and may also act by lessening the nitrogenous waste products which are sometimes the cause of headache. It is not a very powerful antipyretic or analgesic. In *bacterial infections*, *e. g.*, septicemia, it would seem to be harmful rather than helpful, for it depresses vitality and checks phagocytosis. For *uterine effect* it is employed in menorrhagia and uterine inertia. Among *skin diseases*, it has been recommended internally in pemphigus, exfoliative dermatitis, and pityriasis rubra.

In *blackwater fever*, Cardamitis says that quinine does more harm than good. He cites 1347 cases treated by quinine, with 24.42 per cent. of deaths, and 1134 treated without quinine, with 7.32 per cent. of deaths.

In *pneumonia*, Solis-Cohen uses 15 grains (1 gm.) of quinine and urea chloride hypodermatically, repeated every two or three hours for 2, 3, or 4 doses. The fever disappears by lysis instead of by crisis. Before acceptance, this requires extensive clinical testing.

In *malaria* it is practically specific. In tertian or quartan malaria, about two or three hours after a large dose of quinine, the parasites in the red cells can be seen to have lost their ameboid motions, and they soon become granular and die. The quinine acts most strongly on the forms just breaking into spores and on the free-swimming organisms; and as these are present in the blood about the time of the chill, the quinine, on account of its rapid absorption and rapid excretion, is best given just at this time. Fifteen grains (1 gm.) may be administered just before, during, or after the chill, and it should be followed by 5 grains three times a day for one or two months. In malarial regions quinine is taken in large quantities (1 dram) as a prophylactic; it is rapidly excreted. There is much evidence to show that it does reduce the number of cases in a malarial community, and does not seem to do any harm to the takers. In pernicious malaria the bimuriate of quinine and urea in 10 per cent. solution has been employed up to 100 grains in a day, but recovery from this condition is rare in any case. Brewster reports the intravenous administration in pernicious malaria of 100 grains in six hours without untoward effects.

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the increase in the number of leukocytes, but von Noorden states that "of salicylic acid and its products, one can say positively that they favor the elimination of uric acid in gouty subjects."

Excretion is by the kidneys, chiefly as salicyluric acid, a glycocoll compound which gives a violet-red color with ferric chloride. Traces are also found in the bile, milk, and sweat. The appearance in rheumatic and other inflammatory exudates has been referred to above.

The *kidneys* may be irritated by large quantities, and diuresis sometimes results. But among drugs of this class salicylic acid is a comparatively safe one, for quite frequently 100 or 200 grains a day of sodium salicylate have been given without signs of kidney inflammation. Von Noorden, however, warns against possible kidney effects in gout.

Toxicology.—The early signs of overdosage are: nausea, vomiting, and sometimes diarrhea; or headache, ringing in the ears, and deafness; or mental excitement. As judged by these signs, Hanzlik (1913) found that for human adults the toxic amount of sodium salicylate is about 200 grains (13 gm.), of methyl salicylate and aspirin about 120 grains (8 gm.), and of diplosal, 100 grains (6.7 gm.).

When the symptoms resemble those of cinchonism, the condition is known as salicylism; when there is mental excitation, it is known as salicylic intoxication, or "salicylic jag." Salicylism is characterized by fulness in the head, headache, mental dulness and apathy, with ringing in the ears, deafness, disordered vision, and muscular weakness. The ear symptoms are not so common as from quinine, and are due either to congestion or anemia or to degeneration of the nerve-elements of the cochlea. Scheyer reports a case of labyrinthitis with permanent impairment of the hearing. The eye symptoms are also associated with circulatory changes in the retina or degenerative changes in retina or optic nerve.

In the salicylic intoxication the cerebral symptoms resemble those from atropine. The patient is talkative and very cheerful, and may pass on to delirium with hallucinations, motor activity, and attempts to get out of bed.

Very large doses produce weakness of the heart and depression of the respiratory and vasoconstrictor centers, with collapse. But the writer has frequently seen 20 grains of the sodium salicylate given every two hours, and occasionally 30 grains, without any noticeable effect on the heart's action or the blood-pressure. Hanzlik found no especial tolerance for the salicylates in acute rheumatism. (Although phenol and salicylic acid are closely

water and freely in alcohol. It gives no reaction with ferric chloride, unless previously decomposed by alkalies or boiling with water. On boiling with 10 per cent. sodium hydroxide solution it separates into its components. The claim is made that it passes through the stomach unchanged, and is decomposed in the alkaline intestinal contents to form sodium salicylate and sodium acetate; but sodium carbonate in a test-tube does not so decompose it. Theoretically, it should not be given with sodium bicarbonate or other alkali, lest it be decomposed in the stomach; but in the author's experience the bicarbonate lessens the nausea and heartburn which sometimes result from the drug.

In many instances it has proved less irritant to the stomach than either salicylic acid or sodium salicylate, but not infrequently it causes hyperacidity with heartburn, or nausea or vomiting.

Aspirin has greatly replaced quinine in the affections of the profession and the laity, and is prescribed or taken in 5-grain (0.3 gm.) tablets or capsules every two or three hours for colds, sore throat, neuralgia, headache, and influenza. It is also used wherever a salicylate is indicated. Williamson (1902) found that it reduced the sugar in the urine in a number of cases of diabetes, but not in the severe cases. It is strongly diaphoretic.

Toxicology.—There are a number of reports of angioneurotic swelling of the face and throat, or general urticaria, with or without nausea, vomiting, dizziness, and collapse. These are due to idiosyncrasy, and have usually followed small doses, such as 15 grains (1 gm.). Von Noorden (1912) says that in three of his cases acute nephritis followed the use of aspirin.

Novaspirin is the methyl-citric-acid ester of salicylic acid; **diplosal** is the salicylic-acid ester of salicylic acid; and **diaspirin** is succinyl disalicylic acid. It is claimed for all these that they pass through the stomach unchanged.

Salol, or phenyl salicylate, $C_6H_4.OH.COOC_6H_5$, is in the form of crystals with a characteristic aromatic odor. It gives a violet color with ferric chloride. It is soluble in alcohol, but is insoluble in water and practically insoluble in the gastric juice. In a test-tube alkalies produce the odor of phenol, and in the alkaline contents of the intestine it is decomposed and goes into solution as sodium salicylate and phenol. These products are rapidly absorbed and are excreted in the urine as salicyluric acid and phenol sulphonates. Whether or not they have an antiseptic effect in the intestine is a moot question, most observers, with the exception of Herter, perhaps, having failed to note a diminution of the indican, or any other indication of diminished putrefaction. Indeed, phenol itself, judging from the work of Richards and

Solution	Streptococcus			Bacillus Typhosus	After What Time in Minutes
				0	One.
				6,000	One.
				1,000	Thirty.
				0	One.
				2,000	One.
				10,000	One.
				0	Thirty.
			6,000	∞	One.
			4,000	∞	Thirty.
			300	1	One.
			0	0	Thirty.
			0	0	One.
			0	0	One.
			0	0	One.
			5,000	∞	One.
			200	50	Thirty.
			8,000	4,000	One.
			8,000	2,000	Thirty.
30 per cent	25	0	2,000	300	One.
50 per cent	0	0	0	0	One.
70 per cent	0	0	0	0	One.
VII. *Miscellaneous:*					
Tincture of green soap	0	0	0	0	One.
Hydrogen dioxide	200	1,000	2,000	0	One.
	0	0	0	0	Thirty.
Thiersch's solution	0	0	5,000	10,000	One.
				0	
	0	0	0	0	Thirty.
Potassium permanganate, 1 : 1000	∞	3,000	∞	2,000	One.
	0	0	2,000	0	Thirty.
Copper sulphate, 1 per cent.	∞	4,000	6,000	3,000	One.
	5,000	2,000	4,000	1,000	Thirty.
Boric acid, saturated (1 : 18)	∞	3,000	10,000	∞	One.
	2,000	2,000	5,000	∞	Thirty.
Potassium chlorate, saturated, 6.6 per cent	∞	3,000	10,000	∞	One
	5,000	2,000	5,000	∞	Thirty.
Glycerin	2,000	6,000	∞	∞	One.
	1,000	4,000	∞	∞	Thirty.
Distilled water	10,000	4,000	10,000	∞	One.

eighteen hours, 1,010,509; after forty-two hours, 3,349,733; and after sixty-six hours, 4,405,000. This was while it was kept packed in a freezing mixture of ice and salt.

Successful cold storage requires the greatest care in the regulation of both temperature and moisture; for example, fresh eggs will stand a temperature of 28° F., but after about three months will freeze at a temperature below 30° F.

II. OXIDIZERS

These act by liberating oxygen, and in their action are themselves quickly destroyed. They are very inferior disinfectants, but are effective deodorizers. They readily and permanently destroy many colors, and are used as bleaching-agents.

1. **Aqua hydrogenii dioxidi,** peroxide of hydrogen, H_2O_2, is a watery liquid, rather unstable, and capable of yielding 10 volumes of free oxygen. The Pharmacopœia states that it keeps better if a pledget of cotton is used to stopper the bottle instead of a cork. It destroys cork, rubber tissue, catgut, etc., and in contact with pus, blood, and other organic liquids splits into water and oxygen, giving off the oxygen so actively that it effervesces and produces a foam. In a cavity without free exit this gas may burrow into the tissues, with extension of the infection. It is a powerful deodorizer, and in dilution with not more than one or two volumes of water, is a valuable germicide. In the experiments of the Hygienic Laboratory (1912) cultures of typhoid bacilli were found sterile after an exposure of two and one-half minutes to 50 per cent. solution. (See also table of Post and Nicoll.) It is much employed as a gargle or mouth-wash, as in diphtheria or pyorrhœa alveolaris, or for deeply furred tongue, and as a surgical cleanser in pus conditions. The author has employed it in the colon in intestinal putrefaction, to check the growth of anaërobic bacteria by liberating oxygen; but it proved too irritating to the bowel. It is also irritant in the throat.

2. **Potassium permanganate,** $K_2Mn_2O_8$, in aqueous solution, at once decomposes when it comes in contact with organic matter, giving up oxygen without effervescence and being reduced to the brown, insoluble potassium manganate. It is a chemic antidote to certain oxidizable poisons, such as morphine, phenol, and hydrocyanic acid, is a local irritant and stimulant, as in persistent sinuses, and in 1 : 10,000 to 1 : 1000 solution, is an antiseptic and deodorizer, as of foul ulcers and foul cancers. The crystals of the concentrated solution have been used with success locally in snake-bite. Von Adelung (1913) advises a 2 per cent. solution in ivy-poisoning.

3. **Sodium perborate,** containing about 9 per cent. of available

[illegible] water, and in warm or moist air gives [illegible] as it unites with water to form hydro- [illegible] oxygen, $H_2O + 2Cl = 2HCl + O$. (See [illegible]

II. DEOXIDIZERS

[illegible] group, viz., sulphur dioxide and sul- [illegible] phite, sodium bisulphite, and sodium [illegible]. The sulphites absorb oxygen to [illegible] will destroy many colors, but these on [illegible] be restored through reoxidation. Fer- [illegible] group, as it takes up oxygen; its chief use [illegible] and cess-pools.

[illegible] formed by burning sulphur, is used [illegible] rooms. It bleaches fabrics, though these [illegible] color on exposure to the air. As a disin- [illegible] ficient, but the New York Department of [illegible] sinfection with eight hours' exposure to the [illegible] phur for each 1000 cubic feet of air-space. [illegible] sinfectant power when used with steam or [illegible] more destructive to fabrics and colors. The [illegible] fective in destroying vermin, but it does [illegible] ks.

[illegible] ALOGENS AND THEIR COMPOUNDS

[illegible] **Hypochlorites.**– Chlorine gas is set free [illegible] in contact with moisture, or it may be [illegible] sulphuric acid to a mixture of equal [illegible] ride and sodium chloride. *Chlorine water*, [illegible] *tion of sodium hypochlorite* (Labarraque's [illegible] as gargles, and a solution of *potassium* [illegible] is used to bleach linen. *Antiformin* [illegible] used to dissolve tissue, blood, pus, and [illegible] of sputum for tubercle bacilli.

[illegible] for the disinfection of the surgeon's [illegible] and then rub them together with a little [illegible] ashing-soda; the soluble sodium hypochlo- [illegible] are generated, and serve as effective skin [illegible] acts as a disinfectant by uniting with the [illegible] orm hydrochloric acid, with the liberation [illegible] irritant gas, and is a powerful permanent [illegible] oying wall-paper, fabrics, etc.

[illegible] $CaCl_2.Ca(OCl)_2$, is commonly known as [illegible] It has been much employed in privies,

cause a dermatitis or a pustular rash. After absorption it may have simply the action of an iodide, or give poisonous symptoms which indicate the presence of unchanged iodoform in the blood. Iodoform poisoning usually manifests itself in one of three forms, the prominent symptoms being—(1) Vomiting; (2) cerebral excitement and delirium; or (3) cerebral depression with melancholia. In each case the outcome may be coma and collapse. The poisoning is usually due to the packing of large cavities with strong iodoform gauze. The symptoms of hyperthyroidism have been reported. In tuberculous sinuses and in the peritoneal cavity in tuberculous peritonitis, a mixture of iodoform, glycerin, and ether, incorrectly called "iodoform emulsion," seems to be of benefit; though the belief that iodoform exerts a specific effect upon the tubercle bacillus has no experimental support. It has also been thought to have a special value in infections by the Bacillus pyocyaneus. To remove the odor of iodoform from the hands, Ricketts recommends vinegar.

V. METALS AND THEIR COMPOUNDS

These combine chemically with albumin to form precipitates of metallic albuminates, which make an impenetrable pellicle. Thus the metallic salts have little penetrating power, and are readily destroyed by the body fluids.

Those most employed as antiseptics and disinfectants are:

Of mercury—mercuric chloride; also, slightly, in ointment form, ammoniated mercury and mercuric oxide.

Of gold—sodium aurate, reported by Verhoeff (1906) as of great efficacy and little toxicity.

Of silver—the nitrate, protargol, argyrol, etc.

Of copper and iron—the sulphates.

Of zinc—the sulphate and the chloride.

Of aluminium—the acetate, made fresh in solution.

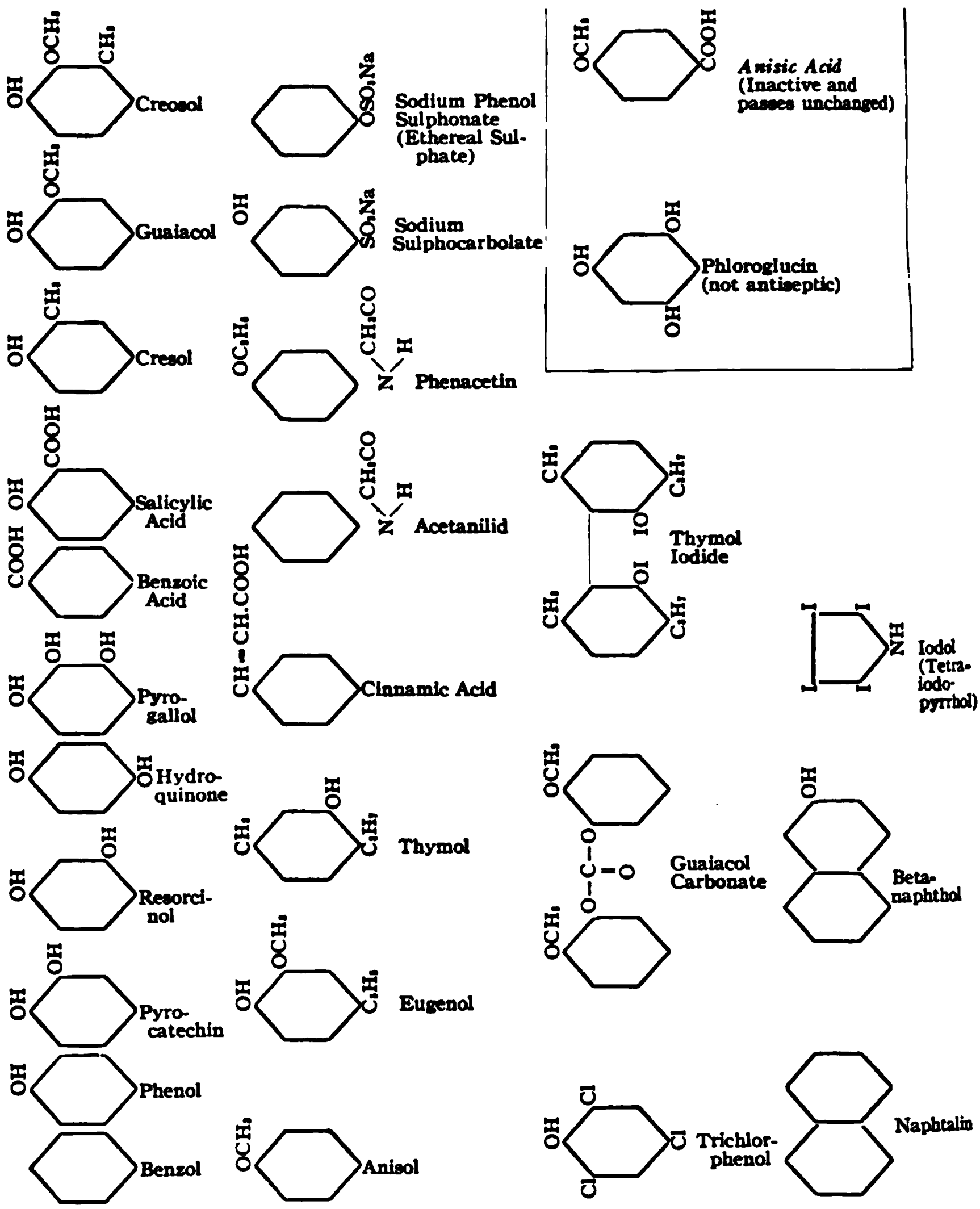
Of bismuth—the subiodide, and perhaps slightly the subnitrate and other salts.

The pharmacology of the metals is considered further on.

VI. MISCELLANEOUS INORGANIC COMPOUNDS

Potassium nitrate (niter or saltpeter), sodium chloride, sodium borate (borax), and boric acid are employed as food preservatives, as in corned beef, ham, butter, etc. Wiley says that the small quantities of salt in butter are not preservative.

Boric acid, a crystalline solid, is soluble in 18 parts of water, 16 of alcohol, and 5 of glycerin, and volatilizes when its solution is boiled. It is soothing locally, and mildly antiseptic. Post and Nicoll (1907) obtained no essential germicidal effect in



Europhen = Cresol iodide.
Losophan = Tri-iodo cresol.

Nosophen = Tetra-iodo-phenolphthalein — Antinosine = Na salt. / Eudoxine = Bi salt.

Guaiacol, the chief constituent of creosote, is an oily liquid, and is used in the same way as creosote; dose, 5 minims (0.3 c.c.). It is also employed as a counterirritant in epididymitis and tuberculous peritonitis. *Guaiacol carbonate* (the carbonic ester) is a solid, and is given in 5-grain (0.3 gm.) capsules. It is tasteless and odorless and is usually well borne by the stomach.

Cresol is much more germicidal than phenol. **Compound cresol solution** (*liquor cresolis compositus*) consists of 50 per cent. of cresol in a solution of soft soap. It is used in 1 per cent. solution in water. Proprietary remedies of similar nature are **lysol** and **creolin.** Fatal poisoning has several times resulted from confusion over the name lysol. At the Hygienic Laboratory the disinfecting value in inorganic solutions as compared with phenol was, for compound cresol solution, 3; for creolin, 3.25; for lysol, 2.12. In solutions of peptone and gelatin, the value for compound cresol solution was 1.87; for creolin, 2.52; and for lysol, 1.57.

Resorcinol (resorcin), readily soluble in water and alcohol, is used in 10 per cent. solution as a scalp wash for dandruff, and in skin lotions as antiseptic and antipruritic. In the stomach it is antifermentative, dose, 5 grains (0.3 gm.). A number of cases of poisoning are reported, even from the application of an ointment.

Pyrogallol turns brown on exposure to air. It is employed in fungous skin diseases. **Tar** and **oil of cade** are added to ointments for chronic eczema and ring-worm. The *syrup of tar* (syrupus picis liquidæ) is used in bronchitis as an expectorant. **Naphthalin** and **beta-naphthol** have a questionable value as intestinal antiseptics; dose, 5 grains (0.3 gm.). Fatalities are reported from a dose of 1.75 gm. of naphthalin given for thread-worms, and from moth-balls eaten by children. The **iodine phenol compounds** are probably antiseptic rather in relation to their phenol constituent than to their iodine; they were brought out as substitutes for iodoform. **Thymol iodide** (aristol) is much employed as an antiseptic dusting-powder.

Volatile Oils.—Eucalyptol is one of the strongest antiseptics in the volatile oil group, but, owing to its oily nature, cannot readily be employed as an antiseptic. Its chief use is as an inhalant in respiratory diseases, coryza, whooping-cough, bronchitis, etc., either with steam or by respirator, or sprayed from an atomizer. A favorite spray consists of about 2 per cent. each of eucalyptol, camphor, and menthol, dissolved in liquid paraffin. *Oil of cinnamon*, *oil of cloves*, and *eugenol* are used by dentists.

Antiseptic solution (liquor antisepticus, U. S. P.) contains

chronic endometritis and chronic pelvic inflammations. Ichthyol has an unpleasant odor, while thiol is nearly odorless.

Internally, ichthyol is employed in cases of intestinal putrefactive toxemia as an intestinal disinfectant, dose, 3 to 5 grains (0.2–0.3 gm.) in a capsule or enteric pill. It is slightly laxative. Ichthyol enters into "Bum Mixture." (See Hoffmann's Anodyne.)

Methylene-blue is little used as an antiseptic. It turns the urine a bluish-green, a fact that has been made use of as a functional test for the kidneys. It has been injected into recurrent or inoperable carcinomata, but without any noteworthy effects. After its ingestion by mouth, Brauer found large quantities of it in the bile. The ordinary commercial article usually contains zinc, and if taken internally, may cause vomiting. The author saw a case of acute gastro-enteritis follow a capsule of methyl-blue, prescribed by the physician in mistake for methylene-blue.

Formaldehyd (HCOH) is a gas, and its aqueous solution, containing not less than 37 per cent. by weight of absolute formaldehyd, is official under the name of "Liquor Formaldehydi." This solution should be neutral or only faintly acid to litmus, showing the absence of formic or other acids. It is marketed under the name of "Formalin," and usually contains about 10 per cent. of methyl alcohol to facilitate solution and prevent polymerization. At ordinary temperature it gives off formaldehyd gas. On cooling the solution below 68° F. and drying, a white powder results. This is known as **paraform** (trioxymethylene), and is a polymeric form of formaldehyd. On gently heating, this is reconverted into gaseous formaldehyd.

Formaldehyd is pungent and very irritating to eyes, nose, and throat. It is rendered inert by alkalies, especially ammonia; it reduces Fehling's solution; it attacks metals (instruments); it hardens tissues, blood, and gelatin (blood on the hands becomes darkened and difficult to wash off). This last property has been made use of to harden gelatin capsules so that they would pass through the stomach into the intestine before dissolving (glutol capsules); but the degree of hardening is uncertain. It is employed as a hardening and fixing agent for anatomic and biologic specimens, and is used as an arterial injection for embalming the dead and for preserving cadavers for dissection. It may be employed for fixing blood-smears. An important property is that of preventing the coagulation of serum albumin by heat, as in urine.

Formaldehyd is a powerful disinfectant. It is much employed as a preservative of foods. One part in 20,000 cannot be detected by its odor, yet will keep milk for several days. In 1:50,000

mouth and jaw. In addition the patient feels ill and there may be headache, lassitude, muscular weakness, and diarrhea; occasionally there is constipation. As a prophylactic during the administration of mercury salts, and as treatment for mercurial stomatitis, a mouth-wash of a saturated solution of potassium chlorate with a little tincture of myrrh is recommended.

2. *Severe acute poisoning* is usually due to the bichloride, either from swallowing the tablets or a solution (often with suicidal intent), or from the retention of strong solutions used as uterine or vaginal douches. Taken by mouth, bichloride gives a strongly metallic and astringent taste. If the swallowed liquid is strong enough, there is local corrosion of mouth, esophagus, and stomach, followed by abdominal pain and vomiting. There may be copious serous or bloody stools, albuminous or bloody urine, or suppression of the urine, delirium, coma, collapse, and death or slow recovery. Postmortem examination shows the local corrosion of the upper part of the alimentary tract, and also acute colitis, acute proctitis, and acute nephritis. In the enterocolitis there may be extensive necrosis; in the nephritis there are fatty degeneration and necrosis of the cells of the convoluted tubules. Pericarditis is reported. There is occasionally a period of a day or two before the onset of the symptoms.

If the patient does not die quickly, he may be ill for days or weeks, with marked salivation, inflammatory and gangrenous lesions of the pharynx, cheeks, and hard palate, spongy and broken-down gums, loss of the teeth, gastritis, colitis, and nephritis. He may eventually recover, or may die of uremia or colitis or general prostration. Arterial pressure may be high until collapse sets in. Of five such cases due to antiseptic tablets seen in two years by the author, three died and two recovered.

Treatment.—At the outset, after bichloride is swallowed, white of egg or milk should be given to form non-corrosive albuminates; and these should promptly be removed from the stomach by lavage or vomiting to prevent absorption. Bland oils and other demulcents should then be given to soothe damaged membranes. The systemic treatment is symptomatic. As the mouth, colon, and kidney symptoms develop, these require vigorous treatment. Potassium chlorate and myrrh make a favorite mouth-wash, and if the mouth is foul, peroxide of hydrogen. The colitis and nephritis require the usual treatment for these conditions.

Chronic Poisoning.—This is seen among makers of mirrors, barometers, thermometers, etc. The writer saw a case in a man who had used cinnabar (mercuric sulphide) in an Indian make-up. Besides the salivation, the poisoning shows the usual effects of

Toxicology.—Though lead has but little use in therapeutics, it is of importance to physicians because of the frequency of chronic lead-poisoning or plumbism. This occurs very commonly among painters and plumbers and other workers in lead (type, lead pipe, shot, pottery glazing, enamelware, etc.), and is one of the diseases often met with in clinics and hospitals. It may even result from hair-washes containing lead acetate, from water that has stood in lead pipes, from canned food with lead in the solder of the cans, from wall-paper, or from the prolonged application of plasters (with lead plaster base) to the skin. Gottheil reports a case of death from the sediment (lead sulphate) in Burow's solution made with lead acetate and alum.

The symptoms are: Anemia and wasting, foul breath, bad taste in the mouth, loss of appetite, especially in the morning, gastric and intestinal disturbances, pains in the joints and bones, and spots before the eyes. Sailer and Speese found almost complete absence of gastric juice in 10 out of 12 subjects. Chronic nephritis is very common, and the arterial pressure tends to be high. In rabbits, Charteris found that lead carbonate produced a marked anemia, with degeneration of both the leukoblastic and the erythroblastic elements of the bone-marrow. In addition there are usually certain manifestations which are characteristic of lead, and determine the type of complaint to the physician, viz.:

1. *Colic.*—Lead colic, painter's colic—true colic with marked constipation. The patient is relieved by pressure upon the abdomen and will often be found lying prone upon a pillow or bolster. Mosse found that the injection of lead acetate into animals caused degenerative changes in the sympathetic ganglia of the abdomen. And it has generally been believed that the *constipation* is due to irritation of the splanchnic inhibitory nerves of the intestine. But both the constipation and the *colic* are probably due to an irregular irritation of the vagus nerves, the motor nerves of the small intestines, for Oliver found that in animals dead from lead-poisoning the small intestines were contracted tightly at irregular intervals, and Hertz noted by the *x*-rays that the retardation occurs in the small intestine, which is unusual in constipation. It is presumably a spastic constipation. Vaguez (1904) and Pal (1905) found the colic associated with a crisis of general arterial hypertension. Its severity can be lessened by atropine, by opium, or by cathartics, the establishment of coördinated peristalsis apparently aiding in overcoming the spasms. Colic is the most frequently observed of the striking manifestations. It is sometimes followed by a soreness in the abdomen which persists for weeks.

2. *Palsy.*—The usual lesion is a motor neuritis of the musculo-

at one time employed in epilepsy, chorea, whooping-cough, and other spasmodic nervous affections, but are scarcely used internally at present.

BISMUTH

The bismuth (bismuthum) salts commonly employed are the *subcarbonate* and the *subnitrate*, which are white, and the *subgallate*, which is yellow. Dose, 30 grains (2 gm.). They are insoluble in water, are very slightly astringent, and resemble in their action the soothing salts of zinc. But their chief use is in the alimentary tract, where they do not form irritant compounds.

They act in a purely mechanical manner as protectives and demulcents to the mucous membrane of both stomach and bowels. It has been ascertained that if given before irritant emetics, they can prevent vomiting. The author has in a number of instances given bismuth subnitrate with a test-breakfast, and has usually at the end of the hour found a much lessened secretion or acidity. In a few cases the gastric secretion was not changed by the bismuth. It is noteworthy that at the end of the test-breakfast hour the bismuth salt was uniformly mixed with the extracted stomach contents, and that it had changed from a heavy powder to a flocculent substance that settled slowly with the food. Several hours after its administration to dogs the author found the bismuth subnitrate in this same flocculent state, and coating the mucous membrane very uniformly as far as the ileocecal valve. In the colon the bismuth salt becomes black from the formation of the sulphide, and this renders the stools black. As the sulphide forms hard crystals, it sometimes acts as an irritant.

The bismuth salts have come into very extensive use in *x*-ray work, their opacity to the rays making it easy to obtain pictures of the whole alimentary tract. The subcarbonate, the oxide, and the oxychloride are employed for this purpose by mouth or rectum, in amounts of about two ounces, mixed with zoolak, buttermilk, thick soup, etc. The subnitrate is no longer employed in these large amounts, as a number of cases of bismuth and nitrite poisoning have occurred from its use.

In one *x*-ray case of the author's two very large bismuth balls formed in the colon and had to be broken up in the rectum before they could be extracted.

Toxicology.—From the local application to extensive burns, from the injection into tuberculous sinuses, and from the use of it for *x*-ray pictures, bismuth has been the cause of poisoning. Its symptoms resemble largely those of poisoning by the other heavy metals, and are: salivation and stomatitis, with a black

These might be compared with the table given under Disinfectants.

Untoward effects of silver are: (1) argyria, a bluish staining of the skin which is permanent. It may appear in spots (the "spotted boy" of the circus). It usually was the result of the now obsolete treatment of epilepsy and other nervous diseases with silver nitrate.

(2) There is also at times from the local use in the eye a conjunctival argyria. According to Theobald, this is more common from the organic compounds than from the nitrate.

Collargol and argyrol solutions are employed for injection into the ureters to obtain *x*-ray pictures of the ureter and kidney pelvis.

ALUMINIUM (ALUMINUM)

Alum (alumen, aluminis) of the Pharmacopœia is potassium alum, the double sulphate of aluminium and potassium, $K_2Al_2(SO_4)_4.24H_2O$. It is soluble in 9 parts of water and insoluble in alcohol. Its taste is sour, and it is decidedly astringent by coagulation of the proteins of the superficial cells, but it is not very irritant. It is a constituent of some baking-powders, but is, without much doubt, harmful to digestion.

It is employed, usually in 5 per cent. solution, as a gargle or spray in relaxed sore throat, as a vaginal douche, and as a wash for the skin to stop local sweating of the hands and feet or the night-sweats of tuberculosis. The crystals may be used to shrink canker sores in the mouth, or to check hemorrhage from scratches or small cuts. The powdered alum has been used in 60-grain (4 gm.) dose as an emetic, but is not at all reliable.

Burnt alum (alumen exsiccatum) is alum with the water of crystallization driven off by heat. It has a great affinity for water, is powerfully astringent, and is slightly caustic. Its chief employment is as an application to sluggish ulcers.

The solution of aluminium acetate, N. F. (Burow's solution), is made by acting on calcium acetate with aluminium sulphate in solution, the insoluble calcium sulphate being removed by filtration. It is sometimes prepared by mixing solutions of alum and lead acetate, the lead sulphate formed being filtered off. Poisoning has occurred from failure to remove the precipitated lead salt. It is a slightly astringent, slightly antiseptic liquid, the chief use of which is as a wet dressing for infected wounds. Koll (1912) reports great success with it in 42 cases of colon-bacillus infection of the urinary tract.

[illegible] ferrous iodide. dose. [illegible] minim
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[illegible] the latter in pills of aloes and iron. eac
[illegible]

[illegible] Salts.—They are: The *chloride*
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[illegible] the hypophosphites. These miner
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[illegible] the teeth the dose should be well dilute
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[illegible] contains free acid and is especial
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[illegible] Acids.—These are the ferric acetat
[illegible] Favorite preparations are: *Liquor fe*
[illegible] Basham's mixture, dose, 2 drams 8 c.c.
[illegible] alkaline salts, *iron and ammonium citra*
[illegible] *citrate*, and *iron and potassium tartra*
[illegible] gm. The *citrate of iron and quinine*, dos
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[illegible] *quinine*, containing 1 per cent. of stryc
[illegible] gm., are also official. There are tw
[illegible] *iron*, containing 1 per cent. of iron a
[illegible] the bitter wine of iron, *vinum fe*
[illegible] per cent. of iron and quinine citrate, ea

contains from $\frac{1}{50}$ to $\frac{1}{55}$ grains of iron, enough to make a two-inch nail. The ordinary diet contains $\frac{1}{10}$ to $\frac{1}{5}$ grain (5 to 10 mg.) of iron per day, this minute amount being sufficient to maintain the iron equilibrium of the body. During the growing period more iron is necessary. In human milk, between the third and twelfth days of lactation, Cameron found 21 mg. of iron in 100 c.c.; while in mixed cow's milk Bunge found 3.5 mg., and Van Slyke only 1 mg. in 100 c.c. Krasnogorsky found the iron of milk more readily absorbed than that of egg-yolk or spinach.

For over a month Charteris (1903) gave normal rabbits a daily hypodermatic of ½ to 1 grain (0.03–0.06 gm.) of an albuminate of iron. They maintained health and gained weight. There was no essential change in the bone-marrow except a slight increase in the leukoblastic elements. Therefore, in health, though the administration of iron results in some accumulation of iron either free in the blood or stored up in the liver, spleen, etc., it is not followed by an increase in either the hemoglobin or the red cells, and the iron is in a sense a foreign body; that is, it does not go to form blood, and there is no plethora established. But after bleeding, animals have been shown to utilize iron that was given them, and in many human cases with hemoglobin below normal its administration seems to be followed by a greater increase in both the hemoglobin and the red cells than comes from the food alone. In these cases it is possible that "under the stimulus of iron the blood-forming organs become active in the synthesis of hemoglobin" (von Noorden).

Hemoglobin itself, as in raw blood or uncooked meat, is converted by the gastric juice to acid hematin, and when taken by man is believed to be mostly unabsorbed. It has been ascertained that 1 c.c. of blood by mouth will give a test in the feces. However, Halliburton's experiments with raw blood on rats fed on an otherwise iron-poor diet, showed a slight increase in the red blood-corpuscles and hemoglobin of the blood, and the presence of absorbed iron in the cells of the duodenal mucous membrane.

In cooked blood, as in cooked meat, the hemoglobin is changed and is absorbed more readily, but even then not readily.

Toxicology.—In excessive amounts iron may produce nausea, vomiting, constipation, and headache. Dixon says that if it is administered intravenously it is as toxic as arsenic. In very large quantities the irritant inorganic salts may cause great irritation of stomach and bowels, with collapse. There is no satisfactory evidence that excess of iron has any power to increase a hemorrhagic tendency or to bring on plethora.

Therapeutics.—The therapeutic classification given above indicates its uses. As a *hematinic* it may be employed in all con-

Solution of arsenous acid, liquor acidi arsenosi, 1 per cent., is acid with hydrochloric acid. Dose, 3 minims (0.2 c.c.).

Fowler's solution, *liquor potassii arsenitis*, $KAsO_2.HAsO_2.H_2O$, 1 per cent., contains the compound tincture of lavender to give it distinctive odor, taste, and color as a preventive against accidents. Dose, 3 minims (0.2 c.c.). This is the favorite liquid preparation. It is incompatible with acids, and tends to oxidize and deteriorate.

Arsenic iodide, AsI_3; dose, $\frac{1}{12}$ grain (0.005 gm.).

Donovan's solution, *liquor arseni et hydrargyri iodidi*, contains 1 per cent. each of arsenous iodide and mercuric iodide. Dose, 2 minims (0.12 c.c.).

(*b*) *Those of Arsenic Acid.—Sodium arsenate*, $Na_2HAsO_4,7H_2O$; dose, $\frac{1}{12}$ grain (0.005 gm.).

Dried sodium arsenate, *sodii arsenas exsiccatus*, is sodium arsenate deprived of its water of crystallization by heat. As this water constitutes about two-fifths of the arsenate, the drying nearly doubles the strength. Dose, $\frac{1}{20}$ grain (0.003 gm.).

Solution of sodium arsenate, 1 per cent. of the dried salt; dose, 3 minims (0.2 c.c.).

(*c*) Besides the official preparations, there are a number of *organic compounds* that are in use:

Sodium arsanilate (sodium aminophenyl arsonate) is employed in the form of *atoxyl*, $C_6H_4(NH_2).(AsO.OH.ONa) + 3H_2O$, containing 3 molecules of water of crystallization and 26 per cent. of arsenic; and *soamin*, $C_6H_4(NH_2).(AsO.OH.ONa) + 5H_2O$, which contains 5 molecules of water of crystallization and 22 per cent. of arsenic. They are white powders, soluble in 5 or 6 parts of water, and decomposed by acids. Because of the acidity of the gastric juice, they are given hypodermatically. Dose, ⅓ to 3 grains (0.02–0.2 gm.) every second day.

Arsacetin is sodium acetyl arsanilate, $C_6H_4(NHCH_3CO).(AsO.OH.ONa)$, soluble in 10 parts of cold water and 3 parts of hot water. It can be sterilized in the autoclave at 130° C. for one hour without decomposition. The claim is made that it is not split up by acids. The hypodermatic dose is 3 grains (0.2 gm.) two or three times a week. By mouth the dose is ¾ grain (0.05 gm.) three or four times a day.

Arsenophenylglycin, $As_2(COOH.CH_2.N.H.C_6H_4)_2$, has a hypodermatic dose of 12 grains (0.8 gm.).

Sodium cacodylate, the sodium salt of dimethyl arsenic, $(CH_3)_2AsO.ONa + 3H_2O$, is readily soluble in water. It liberates arsenic quite slowly, hence is less toxic and less active than the inorganic salts. Dose, 1 grain (0.06 gm.) hypodermatically, or 3 grains (0.2 gm.) by mouth daily. A hypodermatic of 4 to 6 grains (0.25–0.35 gm.), repeated in four days, was recommended by John

the stomach with fair rapidity
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sts essentially of erythroblastic and
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Absorption tak[illegible] sex-
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permanganate. Oils should not be employed unless promptly washed from the stomach.

Chronic poisoning is to be seen among the makers of matches. Its chief manifestation is "fossy jaw," a condition of necrosis of the jaw bones which is incurable, and often necessitates extensive curetage of the parts to check the horrible cadaverous odor. It may even require removal of the entire maxilla. Charteris laid bare the periosteum of the lower jaw of rabbits, and repeatedly exposed them to phosphorus fumes, but could not get necrosis.

Therapeutics.—Phosphorus has been used in dose of $\frac{1}{100}$ grain (0.0006 gm.) in the treatment of rickets and osteomalacia. It is given in the form of a pill, an elixir, or a 1 per cent. solution in olive oil. It is probably mostly inert.

The hypophosphites (Na_2PO_2, $CaPO_2$, etc.) have been much employed as nerve tonics. The belief that they furnish phosphorus to the nerve tissues is negatived by the fact that they pass unchanged through the system, and can be almost entirely recovered from the urine as hypophosphites. The *compound syrup of the hypophosphites* is official, dose, 2 drams, which contains $\frac{1}{70}$ grain of strychnine, $\frac{1}{8}$ grain of quinine, and iron and manganese. The strychnine and iron are the essential constituents.

The Glycerophosphates.—Calcium glycerophosphate, $CaPO_4.C_3H_5(OH)_2$ is soluble in 20 parts of cold water; the sodium salt, $Na_2PO_4.C_3H_5(OH)_2$, is very soluble in water and is deliquescent. It is to be obtained only in 50 per cent. solution. They are esters of phosphoric acid, and their administration results in an increase in the urinary phosphates. They are at the present time much in use as general "nerve tonics," and have largely replaced the useless hypophosphites. But there is no satisfactory evidence that they increase the phosphorus in the nervous tissues, and there is abundant evidence that the body can get its needed phosphorus quite as well from the inorganic phosphates; at least this is the case in hens and ducks, which give out a large amount of phosphorus in their eggs in the form of lecithin. Fingerling tried to enrich the milk of goats by the administration of phosphorus compounds. He found that, even when the food was deficient in phosphorus, the organic phosphorus compounds exerted no more favorable influence than the inorganic ones.

There are no pharmacopeial preparations, but the National Formulary gives an elixir containing 1 grain (0.06 gm.) of sodium glycerophosphate and ½ grain (0.03 gm.) of calcium glycerophosphate in each dram (4 c.c.).

resulting in death. The serious eruptions usually occur in patients with much lowered vitality, and especially in those with chronic nephritis.

2. *Mucous Membranes.*—The mucous membranes chiefly irritated are the conjunctivæ and those of nose, throat, bronchi, and stomach. A not unusual effect is that of a severe cold in the head, with watery, injected eyes, headache, and general malaise; there may be, in addition, nausea, salivation, and tender teeth and gums. The patients think they have influenza. A number of cases of edema of the glottis have been reported, also purpuric eruptions on the mucous membranes, and inflammation and swelling of the parotid glands.

It has been ascertained by extensive clinical experience that the minor eruptions are more frequent from the smaller doses of 5 or 10 grains, and that they sometimes disappear when the dose is increased.

Prophylactic measures against the lesions of skin and mucous membranes are great cleanliness of skin and mouth, alkalies, and arsenic. Some think that the sodium iodide is less irritating than the other salts.

Iodide Fever.—In a case of plumbism, Oliver reports a temperature of 101.8° F., and albumin in the urine from 5-grain doses of potassium iodide. In a case of chronic rheumatism of the author's (1912) 10 grains of potassium iodide three times a day caused swelling and intense burning of the face and hands, fever, and eventually delirium. It was learned that the same phenomena had followed iodide the previous year. Konried reports two cases of iodide fever, one of them being from the local use of an ointment.

Chronic iodism is a state in which there are anemia and emaciation, nervousness, tachycardia, and loss of sexual power. Much iodide, even without any poisonous symptoms, tends to lower the body tone and to depress the spirits.

Therapeutics.—Iodides are believed to be more or less specific in tertiary syphilis and actinomycosis. According to Jonathan Hutchinson, "Over the tertiary manifestations of syphilis, the gumma, whether of skin, cellular tissue, coats of arteries, cerebral meninges, or periosteum, potassium iodide exercises almost as definite an influence as mercury over the earlier ones."

Iodides are also employed in:

1. The asthma of emphysema and chronic bronchitis.

2. Arteriosclerosis and some other conditions with chronic connective-tissue production; not in cirrhosis of the liver or chronic nephritis (unless for arterial hypertension).

3. Aneurysm of the aorta.

to colloid has taken place. It is believed that there are many cases of hypothyroidism, with ill-defined symptoms, in which thyroid may be of benefit; but the distinguishing features of this condition have not been satisfactorily determined.

(4) *In Colloid Goiter.* (5) *In Obesity.* (6) *In Rheumatoid Arthritis.* (7) *In Infantile Wasting.* (8) *In Osteomalacia, Rickets, and Delayed Union of Fractures.*

It is contraindicated in the hyperplasia stage of exophthalmic goiter, as it increases the symptoms. (For recent reviews on thyroid, see books on Internal Secretions by Swale Vincent and Biedl.)

Antithyroid Preparations

There are several preparations on the market designed to overcome thyroid hyperactivity. The best known are:

Beebe's serum, a serum obtained from thyroidectomized animals.

Antithyroidin (Moebius) the blood-serum obtained from sheep whose thyroid glands had been removed at least six weeks before. It is preserved with 0.5 per cent. of phenol, and is given by mouth in dose of 8 to 15 minims (0.5–1 c.c.) three times a day.

Thyreoidectin, consisting of gelatin capsules each containing 5 grains (0.3 gm.) of a powder prepared from the dried blood of thyroidectomized animals. Dose, one or two capsules three times a day.

EXPECTORANTS

Expectorants tend to fluidify, consequently to promote the flow of, respiratory mucus. Their action is directly opposed by belladonna. Most of them act reflexly from an irritant (nauseant) action in the stomach. Henderson and Taylor (1910) showed this to be the case with ammonium compounds, antimony, ipecac, and senega. We have considered the ammonium salts, iodide, antimony, and pilocarpine. Others in common use are: Ipecac, 1 grain (0.06 gm.), senega, 15 grains (1 gm.), and aspidosperma (quebracho), 30 grains (2 gm.). In a test-tube the alkalies liquefy mucus but when given by mouth, probably have no effect in the bronchi.

Certain bronchial antiseptics have been mentioned under Antiseptics. Whether or not they act as true expectorants is a question; and whether they are eliminated in the bronchial mucus in sufficient quantity to stimulate the mucous membrane or to act as antiseptics has not been proved. They are: Certain

volatile oil drugs, as oil of turpentine, terebene, pine needle oil, tar, creosote, camphor, cubebs, and garlic, dose, 5 minims (0.3 c.c.) or 5 grains (0.3 gm.); also terpin hydrate, dose, 5 grains (0.3 gm.), benzoic acid, benzoin, balsam of Tolu, and balsam of Peru.

In some cases bronchial activity is promoted by the tonic action of such a drug as strychnine.

Favorite expectorant mixtures are:

1. *The compound licorice mixture*, brown mixture (not Brown's Mixture), which contains licorice, paregoric, wine of antimony, and spirit of nitrous ether. Dose, 1 dram (4 c.c.). It is not a very effective expectorant.

2. *The compound syrup of squill* (Coxe's hive syrup), which contains 8 parts each of the fluidextracts of squill and senega, and 0.2 part of tartar emetic per 100. Dose, ½ dram (2 c.c.) every two or three hours.

3. *Mistura pectoralis*, N. F. (Stokes' mixture), containing ammonium carbonate, 8 grains (0.5 gm.), the fluidextracts of senega and squill, each, 15 minims (1 c.c.), paregoric, 75 minims (5 c.c.) in each ounce (30 c.c.), with syrup of Tolu. Dose, 1 dram (4 c.c.) every two or three hours.

Therapeutics.—To promote the flow of mucus and lessen congestion in the respiratory tract, particularly in the dry stages of bronchial, nasal, or laryngeal inflammation.

IPECACUANHA

Ipecac (*ipecacuanha*) is the root of *Cephaëlis Ipecacuanha* from Brazil, and of the Carthagena ipecac, *Cephaëlis acuminata* (Fam. *Rubiaceæ*), and it is required to yield on assay not less than 2 per cent. of alkaloid. It contains 3 alkaloids—emetine, the important one, and cephaëline and psychotrine.

Preparations and Doses.—The expectorant dose is:

Ipecac, 1 grain (0.06 gm.).

Fluidextract, 1 minim (0.06 c.c.).

Syrup, 7 per cent. (acid with acetic acid), 15 minims (1 c.c.).

Wine, 10 per cent., 10 minims (0.6 c.c.).

Powder of ipecac and opium, 10 per cent., 10 grains (0.6 gm.).

Tincture of ipecac and opium, 10 per cent., 10 minims (0.6 c.c.).

The emetic dose is 15 grains (1 gm.). The dose in amebic colitis is 30 grains (2 gm.), given in enteric pills to prevent vomiting.

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are diarrhea, abdominal
possibly acute nephritis.

Ipecac promotes secret
of the respiratory tract.

Therapeutics.—1. As
powder, with plenty of hot

2. As *expectorant* in d

3. As *nauseant* or emeti

4. *In amebic dysentery*
by many to be specific. I
Philippines. Formerly th
fulness; but it is now given
to give a dose of 30 grains
at the outset, and repeate
the patients escape vomi
Emetine chloride has also
of 2 grains (0.13 gm.), a
¾ grain (0.03–0.045 gm.)
treatment will not only c
hepatitis and prevent the formatic
advises it following operations for
which is not emetic, is useless in a

[redacted] years old gave
[redacted] per side. Those
[redacted] four years

Preparations and I
Ergot, 30 grains
Fluidextract (ace
Extract, 4 grains
Wine, 2 drams (

idly
goo
of
(Ec

goic
gm.
gm
tan

che
the
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Fig. 60.—Ergotized rye (Maisch).

rately, and then mixed
made in the different y
a reaction in the standard amount
three years old required 1 c.c. fo
old 1.5 c.c., and those five years

at degree, if at all,
ries.
he result of large

CARBON MONOXIDE

This gas (CO) becomes of interest from the frequency of its poisoning. Most of the cases result from illuminating-gas, which contains 6 to 10 per cent., and is frequently inhaled with suicidal intent. But some come from defective flues of furnaces, coal stoves, charcoal fires, blast furnaces, and the "after-damp" of mines and old wells.

The gas has great affinity for hemoglobin, and prevents the formation of oxyhemoglobin unless oxygen is present in very great excess. But the compound is not a very stable, one and usually, if respiration is good and oxygen plentiful, splits up so that all the carbon monoxide will be exhaled by the lungs in from one to three hours. The monoxide does not oxidize to carbon dioxide in the body.

The action of the gas is asphyxial, the exclusion of oxygen from the tissues, particularly the central nervous system, being the cause of the symptoms. Haldane found that when mice were placed in oxygen under two atmospheres pressure, so that the plasma would carry enough oxygen to maintain life, carbon monoxide had no toxic effect; but that when the oxygen pressure was removed by exposing the mice to the air, poisoning followed. The toxic symptoms are, therefore, due to an interference with the oxygen-carrying power of the blood.

The symptoms are those of stimulation of the cerebrum and medullary centers, followed by their depression. At first there are headache, dizziness, mental excitement or delirium, slow pulse from stimulation of the vagus center, raised arterial pressure from stimulation of the vasoconstrictor center, dyspnea from stimulation of the respiratory center, and nausea and vomiting from stimulation of the vomiting center. These may be followed by mental dulness or coma, prostration, rapid weak pulse, lowered blood-pressure, slow and shallow or Cheyne-Stokes respiration, fever, loss of control of the sphincters, and convulsions, usually of cerebral (epileptiform) type. The heart continues to beat after respiration has ceased. In the late stages there is sometimes great spasticity or muscular rigidity, so that the patient seems as "stiff as a board." Spiller and others find this associated with bilateral softening of the inner segments of the lenticular nuclei, the softening being due to changes in the minute supplying arteries.

A striking characteristic of the poisoning is a subsidence of the acute symptoms, followed by apparent recovery, and then some hours or days later the appearance of serious disturbances of the central nervous system, showing in mental derangement, paralyses, epileptiform convulsions, or collapse and death.

OXYGEN

Oxygen gas is marketed under compression in steel containers. For administration it is passed through water in a bottle, and conveyed to the patient by tubing terminating either in a nose-piece to be inserted into the nostril, or in a funnel to be held before the face. It tends to dry the mucous membranes, so if continued for any length of time should be accompanied by the steam from a croup kettle.

Action.—The inhalation of oxygen in health has no effect on metabolism, or on the character or depth of respiration, but it regularly reduces the rate of the heart and tends to raise arterial pressure. Bence found that in cases of cyanosis, it reduced the viscosity of the blood; and Stewart noted that, in a case of emphysema, chronic bronchitis, and recurring cyanosis, it increased the blood-flow in the hands from 30 to 70 per cent., though it brought about no especial changes in the respiratory movements.

The tension of oxygen in the alveolar air of man is 107 mm. Hg (Starling), and at this tension the oxygen in the hemoglobin and plasma is about 15.6 per cent. On breathing pure oxygen for a short time the percentage rises to 19.9 per cent. In cases of cyanosis, however, where the CO_2 tension in the blood is high, the capacity of the blood for oxygen is diminished.

Hill and Flack have noted that after hard boxing-bouts of men not in good training, the inhalation of oxygen reduced the pulse-rate almost to normal, abolished the shallow, hurried breathing, and prevented the stiffness of the muscles which otherwise would have followed on the next day. It has been used in other athletic exercises with similar results.

In mountain-climbing, the inhalation of oxygen has proved preventive of "mountain-sickness," which overcomes those not inured to hard work at high altitudes.

Therapeutics.—From the physiologic action, it is evident that the inhalation of oxygen may be of great value in conditions of *cyanosis*, *depressed breathing*, and *failure of the circulation*, whether acute or chronic. Its chief employment has been in *pneumonia*. The author's method in pneumonia is to build a tent over the head and shoulders of the patient, and let oxygen and the steam from a croup-kettle mingle with the air in the tent.

= pound or pounds; O = pint or pints (from octavius, one-eighth of a gallon), and Cong. (Congius) = gallon or gallons. As solids are weighed and liquids measured, it is superfluous to prefix *f* before the dram and ounce signs, as f℥, f℥, to indicate fluidram, fluidounce. The symbol for scruple ℈ is dropping out of use because in written prescriptions it has frequently been mistaken for ʒ (dram).

In printing Roman numerals of prescriptions small letters are employed as: iv = 4, xlviii = 48. In writing, small letters are used for one (i or j), five (v), and ten (x), and capitals for 50 (L), 100 (C), and 1000 (M); and it is customary to draw a line above all the letters making up the number, the dots of i and j being put above this line; for example, $\overline{\text{xviij}}$. In a number with terminal *one*, as one, two, three, seven, or eight, the last letter is printed j, or written as i with a stroke projecting below the line, *e. g.*, ij, iij, vij. This is to signify that it is terminal. Errors have been made because of a comma inadvertently added, and even because of some mark, such as a fly-speck, upon the paper. The dot over the terminal one is an additional check; for if all the letters i and j are not dotted, the pharmacist may be in doubt as to the number intended. As v, x, l and c are not dotted letters, it is incorrect to place dots over them.

In expressing *fractions* in the apothecaries' system, one-half is printed ss, and written ss or *ſs*, the manuscript double s. It is an abbreviation of the Latin *semis*. Other fractions are written in Arabic numerals as vulgar fractions, *e. g.*, $\frac{1}{3}$, $\frac{1}{5}$, $\frac{1}{8}$. Fractions other than one-half are not employed with terms other than grain or minim. Thus, while ʒiss is good usage, ʒi $\frac{1}{5}$ is not, and should be expressed as ʒi gr. xii, or as gr. lxxij.

A typical example of an ordinary liquid prescription is:

For Mrs. Wilson, April 20, 1913.

℞ Bismuthi subnitratis..... ʒij
Misturæ cretæ.....q. s. ad ℥iij
M. et Sig.—ʒij with a little water every three hours.

W. M. Johnson, M.D.

Interpreted, this would read: Take two drams of the subnitrate of bismuth and a sufficient quantity of chalk mixture to make the total measure three ounces, mix them together (according to the art of pharmacy), and on the label write, "Two teaspoonfuls with a little water every three hours."

According to custom, a prescription is written in six sections, viz.:

1. The *name* of the patient and the *date*. (The name is omitted from a prescription for venereal disease, or where it is

This calls for 24 doses, containing 240 minims of the tincture of nux vomica, *i. e.*, each dose contains 10 minims. If this should be written:

℞ Tinct. nucis vomicæ..... ℥ss
Tinct. cardamomi comp..... ℥iij

the total quantity of the prescription would be ℥iiiss, or 28 doses, and each dose of the tincture of nux would be $8\frac{4}{7}$ minims. Another reason for avoiding this type of prescription is that the quantities make an irregular total, and do not fit any standard sized bottle.

Measures.—The measures used by patients are: drop, teaspoon, dessertspoon, tablespoon, sherry glass, wineglass, tea-cup, and glass or tumbler.

Drops.—Drops are uncertain measures, their size differing according to the viscosity of the liquid, the temperature, the fulness of the container, the surface from which dropped, the rapidity of dropping, etc. Drop bottles and medicine-droppers or pipets may be had, but these vary greatly in the size of their orifices, and consequently in the size of their drops. For example, with five medicine-droppers bought at different drug-stores by the writer, 60 minims of the tincture of nux vomica required respectively 200, 172, 167, 142, and 132 drops, while from the shop bottle containing the tincture it took 125 drops. Of commercial droppers, the only one that we know that is made with a standard orifice is the *Barnes Medicine Dropper* (not the Barnes Eye Dropper). With this dropper 60 drops of water measure 60 minims; of other liquids the number of drops varies according to their nature. The drop is, therefore, not a certain measure. We have several times prescribed the Barnes Medicine Dropper and found that the druggist sent instead a dropper with a much smaller orifice.

Approximately, *when dropped from the mouth of a bottle*, aqueous liquids, glycerin, and the fixed oils measure one drop to the minim, volatile oils and strongly alcoholic liquids 2 drops to the minim, ether 3 or 4 drops, chloroform 5 drops, and bromoform 6 drops.

The term minim should not be used in the directions for the patient unless the patient or nurse has a minim glass for accurate measuring.

Spoonfuls.—A medicinal teaspoonful is 1 dram, a dessertspoonful is 2 drams, a tablespoonful is 4 drams; but, unfortunately, the spoons in common use are not made to standard, and hold from 25 to 50 per cent. more than these amounts. Hence if accuracy is important, it is a good plan to advise the use of measuring-

glasses, which may be had at trifling cost correctly graduated on the scale of one dram to one teaspoonful. In lieu of the measuring-glass, DeLorme suggests that we reckon on six teaspoonfuls to an ounce; and he shows how much such a procedure tends to simplify the calculation of quantities in prescriptions. (See below.)

Glassfuls.—A sherry glass holds about 2 ounces, a wineglass about 3 ounces, a glass or tumbler about 8 ounces. A tea-cup holds 5 or 6 ounces.

ADMINISTRATION OF LIQUIDS

Vehicles and Flavors

The **vehicle** is the diluent or solvent. It is generally employed in sufficient quantity to make the dose a readily measurable amount. A vehicle may be—(*a*) non-medicinal, as plain water, or a flavored liquid, or a mucilaginous liquid to hold heavy powders in suspension; or (*b*) it may have medicinal value. It is to be remembered that a prescription is often rendered more palatable and no less efficient through the medium of a pleasant tasting vehicle or an added flavor. The simple vehicles in common use are: water, the flavored waters (anise, cinnamon, peppermint, wintergreen, etc.), alcohol, sherry wine, aromatic elixir, elixir adjuvans (incompatible with acids), and the flavored syrups (citric acid, almond, ginger, wild cherry, orange-peel, orange-flowers, raspberry, rose, tolu, and the compound syrup of sarsaparilla which contains sarsaparilla, licorice, senna, sassafras, anise, and wintergreen).

Flavors.—Small amounts of special flavoring substances, with or without medicinal properties, are frequently added to prescriptions, especially where the vehicle is plain water or alcohol. Such are: (*a*) *Sweetening agents*, as sugar, glycerin, and the various syrups. In diabetes, saccharin, which dissolves in alkaline media, may be employed.

(*b*) *Aromatics*—the waters and spirits (bitter almond, anise, compound spirit of orange, cinnamon, lavender, peppermint, spearmint, and wintergreen), the elixirs, the fluidextract of licorice (incompatible with acids), the aromatic fluidextract (made of cardamom, ginger, cinnamon, and nutmeg), the tinctures of cardamom, cinnamon, ginger, lemon-peel, bitter orange, sweet orange, tolu, vanilla, the compound tincture of cardamom (made of cardamom, cinnamon, and caraway), and the compound tincture of lavender (made of lavender, rosemary, cloves, cinnamon, and nutmeg). Many of the flavored syrups combine sweetening and aromatic properties.

Bitter or unpleasant tastes in liquids may be overcome or partly so by these flavoring substances or by flavored vehicles. Bitterness may be especially overcome by the syrup of yerba santa. (See Part II.) Bitter or disagreeable solids are sometimes made up into flavored liquid mixtures.

Colors are sometimes added to watery-looking liquids for their psychic effect. The preparation seems more like "real medicine," and if it is a powerful remedy, is less likely to be mistaken for something harmless. Colored aromatic tinctures, like the compound tincture of lavender, may be employed, or tincture of persio, or carmine (in aqueous liquid).

(For definitions of the classes of liquids employed, see Part I.)

ADMINISTRATION OF SOLIDS

The regular diluent for powdered drugs dispensed in very small quantities is sugar of milk. Of drugs in tablet form, the tablet triturates are made with sugar of milk, hypodermatic tablets with cane-sugar, and compressed tablets without any diluent except in a few cases where it is necessary to increase the cohesive properties of the powder.

For pills, the ingredients must be worked together into a mass, which is then divided equally into the requisite number of parts. These parts are then given a round or elliptic shape. The pills must be plastic, to permit their shaping, but they must be firm enough to retain their shape on standing.

An **excipient** is a substance employed to give proper consistence to a mass. It may be water, glycerin, glucose, syrup, glycerite of starch, extract of gentian, etc. The choice of excipient should be left to the pharmacist. For oxidizable substances, as silver nitrate or potassium permanganate, the diluent should be an inert powder, such as kaolin, and the excipient an inert substance, like petrolatum.

Pills may be rolled in some powder, such as starch or lycopodium, to prevent their sticking together, or they may have a special coating. The more common coatings are gelatin, sugar, and silver. Pills intended to pass through the stomach unchanged, but to disintegrate in the intestine, are known as "enteric" pills, and are usually coated with *salol* or *keratin*. These coatings are insoluble in the acid gastric juice, but dissolve in the alkaline intestinal contents. The so-called chocolate-coated pills are really only gelatin or sugar-coated pills with chocolate color. The objects in coating pills are: to improve their appearance, to improve their keeping qualities, to hide their taste, or to make them "enteric."

To hide a bitter or unpleasant taste, powders may be dis-

writing may be accomplished with very little knowledge of the language; for the construction follows rules that are not always those of classic Latin; and the customary methods of abbreviation enable one, without fear of criticism, to omit a Latin ending if the correct one is not known. Approved prescription writing, however, requires some knowledge of Latin and a familiarity with certain rules. The following information about Latin words is not given with any intent to teach that language, but solely with the desire to facilitate prescription writing for those who do not know Latin.

NOUNS

A general rule for case-endings in the name of ingredients is: *The name of the substance or the class of remedy takes the genitive ending when the quantity is a weight or measure; and the accusative ending when the quantity is a number.*

The *genitive case* is the possessive, implying the preposition "of." For example, ℞ Syrupi scillæ compositi, ℥ij, may be translated literally "Take (thou) 2 ounces *of* the compound syrup of squill." ℞ Acetanilidi, gr. xxx, is "Take 30 grains of acetanilid." The object of the verb "recipe" in these cases is the word for ounces (uncias) or grains (grana), the plural accusative.

The *accusative case* represents the object of a verb. When the quantity is a number, this number is a numeral adjective; and the object of the verb *recipe* is the name of the numbered objects. For example: ℞ Capsulas acetphenetidini, āā gr. v, No. xij—"Take 12 capsules of phenacetin, each of 5 grains." That is, "Capsulas" is the object of the verb recipe. The term *No.* (numero) is customarily placed before numbers of this kind. It may be translated "in number." Thus the prescription might be read: "Take capsules of phenacetin, each of 5 grains, and in number, 12." The genitive singular ending is the one most required, and this, with the accusative singular and plural, are all that need be learned. The case-endings of nouns used in prescriptions are:

	Singular		Plural
	Gen.	Acc.	Acc.
1. Of nouns ending in *a* (fem.), as quinina....	ae	am	as
2. Of nouns ending in *us* (masc.), as strophanthus.....	i	um	os
3. Of nouns ending in *um* (neuter), as chloralum.....	i	um	a
4. Almost all other nouns.....	is	em	es (masc.) es (fem.) a (neuter)

writing may be accom[illegible] [illegible] exsiccatus (dried),
language; for the const[illegible] [illegible] granulatus (granu-
those of classic Latin; [illegible] inspissatec . magnus
tion enable one, withou[illegible] ponderosus (heavy),
if the correct one is n[illegible] prepared . purificatus
however, requires som[illegible] [illegible]ductus (reduced), rubrus
certain rules. The [illegible] warm), unus (one). Duo
is not given with any [illegible]
with the desire to fa[illegible] [illegible]oun are: syrupus aromati-
do not know Latin. [illegible]earia parva, pilulas cathar-
[illegible] pulveris glycyrrhizæ com-

[illegible]ne and feminine), *e* (neuter).

A general rule f[illegible] [illegible]ral es.
is: *The name of th[illegible]* [illegible]al id.
genitive ending whe[illegible] [illegible] animalis (animal), dulcis
accusative ending w[illegible] [illegible] glacial), levis (light), mitis
The *genitive ca[illegible]* [illegible]ery, simplex, icis (simple),
"of." For exam[illegible] [illegible]res three), vegetabilis (vege-
translated literall[illegible] [illegible]ding in *ens* have genitive *entis*.
syrup of squill." [illegible]stringens (astringent), bulliens
acetanilid." Th[illegible] [illegible]ervens (hot), recens (fresh),
the word for oun[illegible] [illegible]e noun are: succi limonis
tive. [illegible]ulcis, hydrargyri chloridum
The *accusati*[illegible] [illegible] may modify nouns of another
quantity is a n[illegible] [illegible]ing of its own declension.
the object of th[illegible]
For example:
"Take 12 cap[illegible]
"Capsulas" [illegible] **SER WORDS**
(numero) is [illegible]s, there are employed in the
It may be [illegible] [illegible] for the label a few special
might be rea[illegible] [illegible]ey are:
and in numl[illegible] [illegible] bulliant (let it or them boil),
most requir[illegible] [illegible]strained), detur, dentur (let it or
are all that [illegible] extende supra (spread upon),
prescription [illegible] filtra (filter), misce (mix),
[illegible] write), solve (dissolve), tere

[illegible] immediately; at once).
[illegible] up to, ante (before), in (into),
[illegible] the accusative. After a transi-
[illegible] and expresses the English
[illegible] divide into capsules). After an

1. Of nou[illegible]
2. Of n[illegible]
th[illegible]
3. Of n[illegible]
rat[illegible]
4. Alm[illegible]

℞ Buchu ..... ʒiv
Matico ..... ʒij
Aquæ ..... q. s. ad ℥viij
Ft. infusum.
Sig.—ʒij in a wineglass of water every four hours.

In special cases directions for compounding may be placed after a portion of the ingredients, as:

℞ Peponis ..... ʒij
Granati,
Cusso ..... āā ʒj
Aquæ bullientis ..... q. s. ad ℥j
Ft. infusum, cola et adde—
Oleoresinæ aspidii ..... ʒj
Mucilaginis acaciæ ..... ℥ss
Aquæ ..... q. s. ad ℥viij
Sig.—Take half statim and half in three hours.

II. Objects to be Counted.—*1. Commonly Kept Ready-made—*

(*a*) *With standard name*, or with only one ingredient:

℞ Pilulas catharticas compositas ..... No. iij
Sig.—Take at bedtime.
℞ Capsulas quininæ sulphatis, gr. v ..... No. xij
Sig.—One t. i. d. p. c.

(*b*) *With no standard name—*

℞ Olei ricini ..... ♏iiss
Salolis ..... gr. iiss
M. et ft. capsula No. j. Mitte tales No. xx.
Sig.—One q. 4 h.

(This omission of multiplication should never be resorted to except for ready-made objects. It would suggest a lazy physician.)

2. To Be Made Up Extemporaneously—

℞ Acetanilidi ..... gr. xxx
Ft. chartæ No. vj.
Sig.—One q. 3 h.
℞ Strychninæ sulphatis ..... gr. ¼
Acetphenetidini ..... gr. xxiv
Acetanilidi ..... gr. xvj
M. et ft. capsulæ No. viij. (Or M. et ft. in capsulas No. viij.)
℞ Aloes purificatæ ..... gr. xviij
Massæ hydrargyri ..... ʒss
Olei menthæ piperitæ ..... gtt. iij
M. et ft. pilulæ No. xij. (Or M. et ft. in pilulas No. xij.)
Sig.—Two at bedtime once a week.

The first example of this section may also be written—

℞ Chartas acetanilidi gr. v (or "āā gr. v") . . No. vj.
Sig.—One q. 3 h.

The accusative plural forms of the names of objects to be

abbreviation *Tr.* should not be employed for tincture, as in script form it has frequently been incorrectly read *Fe.*—*i. e.*, fluidextract.

(*b*) In modifying adjectives, as *æq.* for æqualis, *comp.* for compositus, *ppt.* for præcipitatus, *recent.* for recentis, *sat.* for saturatus.

(*c*) In amounts—*q. s.* for quantum sufficiat (as much as may be required), āā for ana (of each), and the regular symbols of weights and measures.

(*d*) In prepositions—c̄ for cum, s̄ for sine.

II. In the Directions for Compounding.—(*a*) In nouns and adjectives, as cach., chart., pil., suppos., tab., tab. trit., tab. hyp., troch., scat. (scatulam = a box), dos. tal. (doses tales = such doses).

To express the kind of coating for pills write *argent.* (argentiferus) = silver-coated, *sacchar.* (sacchariferus) = sugar-coated, and *gelat.* (gelatiniferus), or *g. c.* = gelatin-coated, after the term for pill. The terms "keratin-coated" and "salol-coated" are best written in English. To order that powders should be put in waxed papers, write for *chart. cerat.* (chartas ceratas). Such are used for efflorescent or deliquescent drugs, and for the latter especially if the patient is to be at the seashore or aboard ship.

(*b*) In verbs—ft. for fiat or fiant (let it or them be made), div. for divide (divide), M. for misce (mix), S. or Sig. for Signa (label), bull. for bulliat or bulliant (let it or them boil).

An example of the use of these abbreviations might be: Ft. pil. argent. No. xij (Fiant pilula argentifera, numero duodecim) = let twelve silver-coated pills be made.

III. In the Directions for the Label.—(*a*) *Relating to quantity*—gtt. (drop), ʒj (one teaspoonful), ʒij (one dessertspoonful), ʒiv (one tablespoonful), cochl. parv., coch. mag. (cochlearia parva, magna = small or large spoon). The term cochlearia might properly be abandoned.

(*b*) *Relating to the time of taking*—h. (hour), min. (minute); stat. (statim = at once); a. c. (ante cibum = before eating), p. c. (post cibum = after eating); q. h., q. 2 h., q. 3 h., q. 4 h. (quaqua hora = every hour, every two hours, etc.); o. d., b. i. d., t. i. d., 4 i. d. (omne die, bis in die, ter in die = daily, twice a day, three times a day, etc.); o. m., o. n. (omne mane = each morning, omne nocte = each night); M. et N. (mane et nocte = morning and night; also written "mane nocteque," and "a. m. et p. m."); s. o. s., p. r. n. (si opus sit = if there is necessity; pro re nata = when required). In some circles a distinction is made, *s. o. s.* referring to one dose only, and *p. r. n.* to any number, its interpretation being, "whenever needed."

three drops in water three times a day after eating, and increase one drop per dose each day till the dose is ten drops.

9. One ounce of a saturated solution of potassium iodide. Directions: Fifteen drops in a wineglass of water after each meal. (*Solutio, solutionis* (fem.) means a solution of any kind. *Liquor, liquoris* (masc.) is the official title of an aqueous solution of non-volatile substances.)

10. Two drams each of tincture of ferric chloride, glycerin, and water. Place in wide-mouth bottle (*pone in w. m. bot.*). Direct that it be employed to swab the throat every three hours, and order the druggist to send a throat brush and a Seidlitz powder. (The English name, not the U. S. P. Latin name, is regularly employed for the last mentioned.)

11. Three ounces of a saturated solution of boric acid. Directions: Use warm in eye-cup three times a day. Order an eye-cup sent with it.

12. Half an ounce each of oil of turpentine and camphorated oil. Directions: Rub throat twice a day and cover with flannel. Send a mustard-leaf also.

13. Twenty grains of salicylic acid and sufficient flexible collodion to make a quarter of an ounce. Directions: Paint on the corn every night.

14. Two doses, each containing 15 grains of chloral hydrate and 30 grains of sodium bromide, dissolved in cinnamon water. Directions: One tablespoonful with water at once, and the other tablespoonful two hours later if needed.

15. Twenty-four tablespoonful doses of emulsion of cod-liver oil. Direct that the dose be taken three times a day after meals.

16. Take half an ounce of buchu, make into an infusion with five ounces of boiling water, strain, and add two drams of potassium bicarbonate and sufficient cinnamon water to make half a pint. Directions: A tablespoonful every four hours. (How much potassium bicarbonate is there in each dose?)

17. Take half a dram of alum and two drams of lead acetate, dissolve separately in distilled water, mix the solutions, add distilled water to make the total six ounces, and filter. Directions: Keep dressing wet. (Unless directed to filter out the lead sulphate formed, the pharmacist would leave it in and apply a "shake-before-using" label.)

18. Take four ounces of linseed oil, two ounces of syrup of wild cherry, the requisite amount of acacia (the requisite amount = q.s.), and water enough to make an eight-ounce emulsion. Directions: Two teaspoonfuls every four hours.

19. One ounce each of compound tincture of lavender, aromatic spirit of ammonia, and spirit of chloroform. Direc-

tions: A teaspoonful in a wineglass of hot water when needed for flatulence.

20. Two ounces of a solution of nitrate of silver, 10 grains to the ounce. Put in a dark bottle, and label what it is (in a dark bottle = *in vitro nigro* or *in vitro obscuro*).

The following is a facetious prescription, which might be an effective placebo:

℞ Aquæ fontinalis.....gtt. xv
H_2O,
Hydrogenii monoxidi.....āā ℥ss
Illius repetitæ.....℥j
Ejusdem.....℥ij
Nil aliud.....q. s. ad ℥j
M. et Sig.—Ten drops in a wineglass of water every three hours—For nervousness!

B. Ointments.—Write for:

1. Two ounces of cold cream. Directions: Rub into skin night and morning.

2. Fifteen grains of salicylic acid, one dram each of zinc oxide and precipitated sulphur, and sufficient vaseline (petrolatum) to make one ounce. Directions: Apply to skin each night.

3. One and a half drams of oil of cade and zinc ointment enough to make two ounces. Directions: Apply daily to the eczematous area without rubbing.

4. Two drams each of soft soap and balsam of Peru with 1½ ounces of sulphur ointment. Directions: Rub well into itching area twice a day.

C. Powders.—Take 2 drams of magnesium oxide, 4 drams of sodium bicarbonate, and 1 dram of ginger; mix together and place in a box. Directions: A level teaspoonful with half a glass of water at eleven, at five, and at bed-time.

II. PRACTICE IN PRESCRIPTIONS FOR OBJECTS TO BE COUNTED

Write for—1. Thirty five-grain capsules of quinine sulphate. Directions: Three at time of chill, then one three times a day after eating.

2. Twenty-four capsules, each containing 2½ minims of castor oil and 2½ grains of salol. One every four hours.

3. Twelve five-grain tablets of phenacetin. One daily at 4 P. M.

4. Eight one-quarter-grain tablet triturates of codeine phosphate. One for cough when needed. Have name of drug on label.

5. One tube of hypodermic tablets of morphine sulphate, each, ⅛ grain. Put name on label.

[illegible] lime-water. With the latter it mak
[illegible] mercurous hydroxide, and forms "bla
[illegible] used as an application to venereal sor
[illegible] water or alcohol, comparatively ine
[illegible] tissues.
[illegible] *mercuric chloride* (corrosive sublimate)
[illegible] many metallic salts, alkaloidal sal
[illegible] and albumin.
[illegible] lime-water it makes a yellow precipitate
[illegible] forms "yellow wash," employed as a
[illegible] sores. When the mercury salt is in exces
[illegible] chloride.
[illegible] the surgeon's hands, its antiseptic power

[illegible] iodide it forms mercuric biniodide—2 KI
[illegible] The iodide is of a brilliant scarl
[illegible] the potassium iodide. These two sal
[illegible] together to form the biniodide.
[illegible] white of egg or milk, we have the antido
[illegible] chewed.
[illegible] decomposes alum and other sulphat
[illegible] tends to precipitate many organic substance
[illegible] their solution.
[illegible] with alum makes Burow's solution. T
[illegible] sulphate should be filtered off. The pr
[illegible] iodide is lead iodide of a brilliant yellow.
[illegible] make "ink" with tannic acid; (
[illegible] purple colors with compounds of t

may not only precipitate alkaloidal salts, but may change the gelatin coating of a pill or a gelatin capsule to a tough, leathery, insoluble substance. Alcohol may prevent the precipitation of alkaloidal salts by tannic acid, as in tinctures.

Rule 9: *Chloral hydrate* decomposes to chloroform under the influence of strong alkalies; and when mixed with camphor, menthol, thymol, and similar substances, undergoes a physical change to a liquid.

Rule 10: *Alkaloidal salts* are incompatible with—

(*a*) Alkalies—the precipitate is the pure alkaloid.

(*b*) Tannic acid—the precipitate is the insoluble tannate.

(*c*) Iodine, iodides and bromides—the precipitate is the iodide or bromide.

(*d*) Mercuric bichloride—the precipitate is an insoluble double salt.

Quinine in addition is especially precipitated by salicylates and benzoates.

All these precipitates are more soluble in alcohol than water, so may not show in tinctures and other alcoholic liquids.

Rule 11: *Glucosides* are incompatible for the most part with lead acetate and tannic acid, and are decomposed by the mineral acids.

INDEX

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Carbon dioxid snow
Laminectomy
Bone-grafting and transplantation
Nitrous oxid, intratracheal and intravenous anesthesia
Pituitary surgery
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